TMS in working memory research

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Abstract and Keywords

This chapter provides a broad overview of research focused on the use of transcranial magnetic stimulation (TMS), both alone and together with neural recording modalities such as magnetic resonance imaging (MRI) and electroencephalography (EEG), to elucidate the cognitive and neural underpinnings of working memory. It first considers research using TMS to create "virtual lesions" in targeted brain areas, with the goal of establishing the causal role, and sometimes the timing, of the targeted area in specific working memory component processes. Next, it highlights research adopting a "perturb-and-measure" approach, in which TMS is used in conjunction with simultaneous neural recording (e.g., functional MRI or EEG) to assess the role of brain excitability and inter-area connectivity in working memory. Finally, research using TMS to assess the role of neural oscillations in working memory is reviewed. Throughout, the chapter highlights how different TMS modalities can be used profitably to clarify the neural bases of working memory and to effect strong tests of predictions derived from psychological models.

Keywords: working memory, virtual lesion, perturb-and-measure, neuromodulation, entrainment, sensory recruitment, state-based model

Introduction

Working memory (WM) refers to our ability to hold information "in mind" over short intervals and to use this information in service of ongoing cognition and behavior (Baddeley, 1986; Miller, 1960). As such, WM forms a critical component of the cognitive architecture supporting a range of behaviors, from the short-term retention of information, such as the visual appearance of a stimulus or its spatial location (Luck and Vogel, 1997), to language processing (Collette et al., 2000; Martin et al., 1994), mental calculations (Logie et al., 1994), and the retrieval of information from long-term memory (LTM) (Unsworth et al., 2013). Moreover, WM deficits feature prominently in a number of pathological conditions, including schizophrenia (Lee and Park, 2005) and Parkinson's disease (Possin et al., 2008), in addition to being affected by normal aging (Pliatsikas et al., 2018). Given its im-

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portance, understanding the cognitive and neural mechanisms supporting WM processes has been a major focus of research efforts in the cognitive and neural sciences over the last 50+ years (see review in D’Esposito and Postle, 2015).

Much of the research in this area has been conducted within the framework of the multi-component model of WM proposed by Baddeley and Hitch (1974). This model postulates the existence of multiple storage buffers, including the phonological loop and the visuo-spatial sketchpad, that are independent from LTM and are specialized for the short-term retention of different kinds of information (e.g., verbal and visuo-spatial) and controlled by a separate system they called the “central executive” (Baddeley, 1986). Cognitive neuroscience research examining the neural substrates of this proposed system suggested a prominent role for the prefrontal cortex (PFC) in mediating WM component processes, including separate PFC regions devoted to the storage of different kinds of information and executive control functions (Goldman-Rakic, 1995; Petrides, 2000; Ungerleider et al., 1998). More recently, what have been referred to as “state-based” models have gained in prominence. According to these models, storage in WM is realized through the allocation of attention to internal representations, whether semantic, sensory, or motoric. A critical idea underlying this approach is that information in WM exists in different states of activation, depending on the allocation of attention. In a particularly influential formulation of this idea, Cowan (1995) proposed the existence of two distinct states in WM: a capacity-limited state reflecting the activation of items within the focus of attention; and a much larger capacity state reflecting partially activated representations, often referred to as “activated LTM.” A related proposal, known as the sensorimotor recruitment model (D’Esposito, 2007; D’Esposito and Postle, 2015; Serences, 2016), holds that when simple sensory information (e.g., the color or orientation of an object) needs to be held online, brain regions specialized for the perceptual processing of this information are recruited by higher-order parietal and frontal areas implementing attention and cognitive control functions. For information that affords motoric representation, such as spatial position, action-related representations can also be engaged (e.g., Postle et al., 2006b).

Much of the research attempting to elucidate the neural substrates of WM has relied on a correlational approach, in which the role of a particular brain area is inferred from the topography of neural activation observed during task performance. Although this approach has been highly productive, its inherently correlational nature makes it difficult to draw strong conclusions about the causal necessity of a given area in a particular WM process. By directly influencing ongoing brain activity during (or prior to) task performance, it has been suggested that noninvasive brain stimulation methods, such as transcranial magnetic stimulation (TMS), can support stronger inferences regarding causality (Pascual-Leone et al., 2000). This chapter will cover some of the more prominent TMS studies on WM that illustrate the important contributions this approach has made to the WM field.

The earliest applications of TMS to study WM relied heavily on what has come to be known as the “virtual lesion” approach (Pascual-Leone et al., 1999; Walsh and Cowey, 1998), in which TMS is used to transiently alter activity in particular brain areas, with the

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goal of establishing the causal role, and sometimes the timing, of the contribution of the targeted area in the behavior or cognitive process in question. More recently, studies of WM have emphasized the use of TMS together with neural recording modalities to map the distributed cortical circuits mediating WM functions (e.g., Feredoes et al., 2011) or to assess the information content of WM under different task conditions (Rose et al., 2016). Additionally, repetitive trains of rhythmic TMS have been used to modulate activity in targeted areas, with the goal of elucidating the role of neural oscillations in WM. Importantly, these developments have made it possible for noninvasive brain stimulation studies to move beyond a focus on localization of function and to contribute to ongoing efforts to bridge the gap between cognitive theories of WM, on one hand, and research focused on the biological substrates of WM on the other. In this chapter, we will review findings from studies using TMS, both alone and together with neuroimaging, to study the cognitive and neural mechanisms supporting WM for various kinds of information.

TMS studies of working memory

Targeting TMS

Although other chapters in this volume will cover this issue in more detail than we will do here, it is important to emphasize that how one positions the TMS coil on the scalp is an important determinant of study outcome. Perhaps the most systematic assessment of the influence of TMS targeting procedure on cognitive effects—10-20 coordinate-based vs atlas-based vs (subject-specific) structural magnetic resonance (MR)-based vs (subject-specific) functional magnetic resonance imaging (fMRI)-based—is by Sack and colleagues (2009). Less exhaustive, but specific to WM, are two studies by Feredoes and colleagues (Feredoes and Postle, 2007; Feredoes et al., 2007), which establish that TMS is more effective when targeting is guided by the topography of individual subject-specific fMRI blood oxygenation level-dependent (BOLD) responses (e.g., in areas exhibiting load-dependent increases in BOLD during the performance of an object or spatial WM task) vs group-averaged or anatomically defined targets.

The “virtual lesion” approach

One of the primary uses of TMS in cognitive neuroscience has been for transiently altering local cortical activity in healthy individuals, with the goal of determining the role of the targeted area in particular behavioral and cognitive functions. The protocols available for this purpose can be grouped into different categories, depending on when stimulation is applied—*online methods* involve the delivery of TMS *during* the performance of a task, with the goal of disrupting ongoing processing by imposing an exogenously driven pattern of activity to interfere with task-related processing; conversely, with *offline methods*, stimulation is delivered *before or after* task performance. The most commonly used online methods involve the delivery of either single pulses of TMS or short trains of repetitive (r)TMS. Offline methods, by contrast, involve the delivery of rTMS trains, with the goal of modulating activity in the targeted area either prior to or following task performance. In

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each case, task performance in the TMS condition is compared to performance in a baseline (TMS-absent or sham TMS) or control TMS condition, in which stimulation is applied to a control area not causally implicated in task performance. If performance is disrupted or improved in the TMS vs baseline and/or control condition(s), it is inferred that the targeted area plays a causal role in the cognitive process in question.

Studies using these methods have several advantages over traditional lesion studies of cognitive function (for review, see Pascual-Leone et al., 1999). First, given its temporal specificity—the electrical current induced in the brain following each pulse dissipates in < 1 ms (Walsh and Pascual-Leone, 2003) and TMS-evoked electroencephalographic (EEG) activity returns to baseline within ~300–400 ms (see, for example, Rosanova et al., 2009)—either single-pulse TMS or brief trains of rTMS can be used for “temporal dissection,” to assess the timing of a particular area’s contribution to a given cognitive function. Second, unlike lesion studies, in which the performance of an individual with a focal lesion is compared to the performance of nonlesion controls, participants in TMS studies can be run through identical experimental conditions, both with and without TMS, thus serving as their own controls. A corollary to this point is that TMS experiments are typically carried out on neurologically and psychiatrically healthy individuals, and so interpretation of their results is not complicated by possible nonspecific factors related to the neurological or psychiatric condition of the patients. Third, whereas most lesion studies involving groups of patients must contend with variability in lesion size and location, in TMS studies, each subject is targeted in the same way.

Before proceeding to a consideration of how these protocols have been used to study WM, we should note that although the intent with this approach is almost always to produce a “virtual lesion,” concurrent physiological measures indicate that, in most cases, the effect of the TMS is to change activity in ways that are not well captured by the idea of a lesion. For example, although prolonged low-frequency (1-Hz) TMS and continuous theta burst stimulation (cTBS) have been shown to reduce activity in the targeted area for some period of time following stimulation (Boroojerdi et al., 2002; Chen et al., 1997; Di Lazzaro et al., 2005; Huang et al., 2005), Hamidi and colleagues (2009a) have shown that 10-Hz rTMS can either increase or decrease oscillatory power in the alpha band, and produce a commensurate impairment or improvement of performance. Additionally, Gratton and colleagues (2013) have shown that cTBS, generally assumed to reduce cortical excitability, can increase connectivity between the targeted area and other areas. Departures from outcomes predicted by the virtual lesion assumption will be highlighted when they come up in the sections that follow.

The role of frontal and parietal cortical areas in WM

Some of the first studies to use TMS to study WM adopted the virtual lesion approach to clarify the role of particular brain areas in supporting WM functions. This work was conducted in parallel with ongoing neuroimaging and electrophysiological research that suggested an important role for the PFC in various aspects of WM (Fletcher and Henson, 2001; Ungerleider et al., 1998). Although there was general agreement that the PFC was involved in WM, there were substantial disagreements about the organization of WM

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processes within the PFC (Petrides, 1995). According to one view, the lateral frontal cortex supports domain-specific processing, with distinct dorsolateral and ventrolateral cortical regions supporting WM for spatial and nonspatial information, respectively (Courtney et al., 1996; Goldman-Rakic, 1995; Ungerleider et al., 1998). By contrast, an alternative theory proposed that the lateral frontal cortex plays a process-specific role, with more dorsal regions being recruited in tasks that require the active manipulation and/or monitoring of information in WM, as opposed to simple maintenance (Owen et al., 1999; Petrides, 1996; Postle and D'Esposito, 1999).

A general role for the PFC in the short-term retention of spatial information was suggested by an early study probing the effects of delay-period single-pulse TMS on memory-guided saccades (Muri et al., 1996; see also Pascual-Leone and Hallett, 1994). In this study, stimulation was delivered to either the posterior parietal cortex (PPC) or the dorsolateral PFC (DLPFC) at different time points throughout the 2-second unfilled delay period that followed the offset of a briefly presented saccade target. Results revealed that TMS of the PPC decreased the accuracy of memory-guided saccades to the contralateral visual field when applied very early in the delay period (260 ms after saccade target offset), but not at later intervals (360–1500 ms after saccade target offset). Conversely, TMS of the PFC decreased the contralateral saccade accuracy only when applied 700–1500 ms after saccade target offset, but not at earlier latencies. Moreover, a control condition in which the occipital cortex was stimulated resulted in no significant effect on performance. The authors interpreted these region- and timing-specific effects of TMS on saccade accuracy as supporting a role for the PPC in initial sensory processing and saccade programming, and a role for the PFC in the storage of spatial information required to make a memory-guided saccade.

Subsequent studies used TMS to directly assess the proposal that the PFC is organized by information domain. For example, in a study by Mottaghy and colleagues (2002), an offline stimulation protocol was used, in which low-frequency (1-Hz) trains of rTMS were applied in separate sessions to the dorsomedial (DM)PFC, or the DLPFC, or the ventral PFC[1] prior to the performance of a delayed-recognition WM task that required memory for either spatial locations or faces. The results of this study were mixed. Consistent with a segregation of PFC function by stimulus domain, performance of the spatial task was disrupted by rTMS targeting the DMPFC, and performance of the face task was disrupted by rTMS targeting the ventral PFC. Inconsistent with a strong version of this model, however, was the fact that rTMS of the DLPFC disrupted performance in both tasks. Additional studies assessing the effect of rTMS on regional cerebral blood flow suggested that these effects were likely the result of an rTMS-induced reduction in activity in the targeted areas (Mottaghy et al., 2003, 2000).

A different study (Oliveri et al., 2001), carried out at around the same time, found evidence for anatomical segregation by domain of visual WM in posterior regions, but not in the PFC. In it, single pulses of TMS were delivered bilaterally at various delays during the performance of an n-back task for spatial locations and for abstract objects. In one experiment, although TMS of the superior frontal gyrus (SFG) produced slowed reaction times

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(RTs) only in the spatial task, TMS of the DLPFC increased RTs and decreased accuracy in both tasks. In a second experiment, bilateral TMS of the middle temporal cortex produced elevated RTs in the visual-object task, and bilateral TMS of the PPC produced elevated RTs in the visual-spatial task following PPC stimulation. These findings are consistent with the sensorimotor recruitment view that WM storage is supported by posterior regions that also carry out the perceptual analysis of this information. The effects of TMS to the DLPFC were more consistent with a domain general role for this region.

A series of studies from our group, addressing specific questions about verbal WM, illustrates how the stronger inference supported by rTMS can be used to address inconsistent or otherwise equivocal results generated by neuroimaging studies. The theoretical backdrop is the class of models positing that the DLPFC is important for the manipulation of information in WM, but not for its maintenance (Owen et al., 1999; Petrides, 1996; Postle and D'Esposito, 1999). For verbal material, the task used to address this question was delayed recognition of letters, with maintenance operationalized by varying the set size (e.g., retain two vs five letters, a manipulation of “load”) and manipulation operationalized by varying whether subjects were instructed to maintain sets of five randomly ordered letters in the order presented or to “manipulate” them by reordering them into alphabetical order. Although one fMRI study showed greater manipulation-related activity in the DLPFC (consistent with Owen et al., 1999; Petrides, 1996; Postle and D'Esposito, 1999) and greater load-related activity in the posterior perisylvian regions of the left hemisphere (Postle and D'Esposito, 1999), such correlational data could not definitively rule out the possibility that, although manipulation-related activity is higher, the DLPFC might nonetheless also contribute to maintenance. Indeed, the answer provided by fMRI data could vary with the analysis method, with analyses using group-averaging methods producing evidence for load-sensitive activity in the DLPFC (Narayanan et al., 2005), but single-subject analyses failing to do so (Feredoes and Postle, 2007). To address these questions, we carried out two studies, during which we first carried out fMRI scans to identify areas sensitive to manipulation or sensitive to maintenance, then targeted these regions with delay-period rTMS. In a study investigating manipulation, 5-Hz rTMS was delivered during the final 6 seconds of the delay period[2], and rTMS of the DLPFC impaired performance on trials requiring alphabetization of five items, but not on trials requiring their maintenance, whereas rTMS of the superior parietal lobule (SPL) impaired performance on both types of trials (Postle et al., 2006a). In a study of maintenance, delay-period rTMS delivered at 10 Hz had no effect on performance when targeting the region of the DLPFC, showing load sensitivity in group analyses of fMRI data, but it did disrupt performance when targeting regions of the posterior perisylvian cortex identified with single-subject analyses (Feredoes et al., 2007). Thus, these studies provided stronger evidence than could neuroimaging studies alone about WM-related functions supported by different brain areas and helped adjudicate a situation in which different analyses of the same neuroimaging data set produced different results.

In work from our group examining the contributions of frontal and parietal regions to visual (i.e., nonverbal) WM, Hamidi and colleagues (2008) conducted two experiments to assess the effects of TMS on performance of a spatial delayed-recognition WM task, in

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which participants were asked to retain multiple locations in memory over a 3-second delay, then to indicate whether or not the subsequent memory probe matched the location of one of the memory items. In each experiment, they used an online protocol in which thirty pulses of 10-Hz rTMS, spanning the duration of the delay period, were delivered to the parietal and frontal regions—the SPL and DLPFC in Experiment 1, and the intraparietal sulcus (IPS) and frontal eye field (FEF) in Experiment 2. In each experiment, a control area—the post-central gyrus (PCG)—was also stimulated to control for nonspecific effects of TMS. In both experiments, rTMS increased errors on the delayed-recognition task, irrespective of which region was stimulated (i.e., including the PCG). Interestingly, however, a regionally specific effect of rTMS on RT was observed following stimulation of the SPL—RTs were faster when the SPL was stimulated vs the DLPFC, FEF, IPS, or PCG. This behavioral facilitation effect suggests a potential role for the SPL in the maintenance of spatial information in WM (see Luber et al., 2007 for similar findings).

The utility of the “temporal dissection” approach with rTMS is illustrated by a second set of studies carried out by Hamidi and colleagues (2009b), in which subjects performed tests of spatial WM similar to those from Hamidi et al. (2008), but during which the investigators targeted the response period with rTMS (i.e., the first pulse of the train of rTMS was delivered concurrently with the onset of the memory probe). In contrast to when delivered during the delay period (i.e., Hamidi et al., 2008), response-period rTMS disrupted performance when targeting the DLPFC, but not the SPL or PCG (Hamidi et al., 2009b). Taken together, the results of these two sets of studies provide evidence for an important role for the SPL in the maintenance of spatial information in WM, and for the DLPFC in making decisions and guiding actions with this information. This pattern of findings further suggests that some reports of impaired performance on WM tasks by patients with PFC lesions may be due to impairment in the ability to guide behavior with information held in WM, rather than in memory storage per se.

Another study (Mackey and Curtis, 2017) used TMS to study the proposal, derived from theories of sensorimotor dynamics (Andersen and Cui, 2009; Fuster, 2001), that the parietal cortex largely maintains representations of past sensory information whereas the frontal cortex maintains representations of future plans. To test this proposal, Mackey and Curtis (2017) adopted an online protocol in which three TMS pulses at 50 Hz were delivered to specific location-selective subregions of the parietal and frontal cortices during the performance of a memory-guided saccade task requiring short-term storage of spatial location. Prior to the main experiment, stimulation sites for each participant were identified using fMRI and a nonlinear population receptive field mapping procedure (Dumoulin and Wandell, 2008; Mackey et al., 2016). Analyses focused on the effects of TMS on the accuracy of memory-guided saccades toward the remembered target, as well as of the final eye position on which subjects settled after one or more small corrective saccades, which typically occur following a memory-guided saccade. The authors used these two measures to index the quality of the prospective movement plan and the fidelity of retrospective sensory information. Results revealed that rTMS of the superior aspect of the precentral sulcus (PCS) (the putative homologue of the monkey FEF) increased errors in memory-guided saccades, but not final eye position, in the contralateral visual field. In

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contrast, rTMS in a specific subregion of the IPS (IPS2, the human homologue of monkey lateral intraparietal cortex, LIP) produced increased errors in both memory-guided saccades and final eye position in the contralateral visual field. Taken together, these findings are consistent with a role for the frontal cortex in maintaining information relevant to prospective action vs a role for the parietal cortex in maintaining a code for retrospective perception and for the transformation of this information into a motor plan. Interestingly, and consistent with Hamidi et al. (2008), rTMS of the DLPFC caused no observable impairments in either memory-guided saccades or final eye position.

The role of primary sensory and motor areas in WM

Several studies have used TMS to assess the sensorimotor recruitment hypothesis, which, as described earlier in this chapter, holds that storage of sensory information in WM relies on recruitment by attention of brain regions specialized for basic sensory and motor functions. In one study, Harris and colleagues (2002) applied single TMS pulses to the contralateral or ipsilateral primary somatosensory cortex at two different time points during the 1.5-second delay period of a task probing the delayed recognition of the frequency of vibrotactile stimulation delivered to the fingertip. Results revealed a significant disruption of performance following TMS of the contralateral somatosensory cortex—that is, the region of the somatosensory cortex where the stimulus was represented—during the early, but not late, delay period. These findings were broadly replicated in a more recent study by Zhao et al., 2017, which also reported a disruptive effect of single-pulse TMS of the primary somatosensory cortex early in the delay period. Additionally, Harris and colleagues (2002) reported the effects of single-pulse TMS of the primary somatosensory cortex and DLPFC late in the delay period, effects that the authors attributed to the preparation of goal-directed action.

In the domain of visual WM, Rademaker and colleagues (2017) used short trains of TMS to assess the role of early visual cortex TMS in WM for spatial orientation. Observers were required to remember the orientations of four briefly presented gratings appearing in each of the four screen quadrants. Bursts of three TMS pulses at 10 Hz were then applied, either coincident with stimulus offset or midway through the delay interval. The coil was positioned to target early visual cortex TMS at a location that matched the retinotopic location of one of the stimuli in one of the lower visual fields. The precision of recall responses was then assessed for targets overlapping the targeted retinotopic location vs an unstimulated site. Results revealed that early delay-period TMS impaired recall for all targets, whereas mid-delay TMS *improved* recall performance for targets overlapping the stimulation site. This finding of an rTMS-induced facilitation effect suggests an ongoing role for early visual cortex TMS in WM storage, in keeping with the sensorimotor recruitment hypothesis (see also van de Ven et al., 2012 and van Lamsweerde and Johnson, 2017 for evidence suggesting a time-restricted role for early visual cortex TMS in WM).

Finally, a series of experiments by Zokaei and colleagues (2014a, b) tested state-dependent accounts of WM using a “retrocuing” procedure in which, after the offset of two to-be-remembered moving-dot stimuli, a cue presented during the delay period indicated

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which of the two directions of motion was likely to be tested on that trial. Such "retrodictive cues" have been shown to improve performance relative to trials with no cue (see, for example, Griffin and Nobre, 2003 and Landman et al., 2003). In the present case, the retrocuing paradigm was used to assess the effect of TMS on recall precision for items assumed to be inside vs outside the current focus of attention. In one version of the task, a trial started with the presentation of two moving-dot stimuli, which the observer was instructed to remember across a subsequent delay. Following stimulus offset, a retrocue appeared, indicating with 80 percent validity which of the two directions of motion the participant would be required to recall on that trial. The assumption behind this procedure is that the retrocue prompts the transition of the cued and uncued memory representations into either a prioritized state (i.e., it is moved into the focus of attention) or an unprioritized state (outside the focus of attention), respectively. Following retrocue presentation, rTMS was applied to area MT+ (four pulses at 20 Hz, with intensity either above or below a threshold that had been found to disrupt task performance), which has been shown to be critical for the initial sensory processing of direction of motion (see review in Born and Bradley, 2005). Finally, the observer was asked to report the direction of motion of either the cued (prioritized) or the uncued (unprioritized) item, and the precision of recall was assessed. rTMS had the effect of decreasing the precision with which the cued item was recalled and, surprisingly, had the effect of increasing the precision of the uncued item. The authors reasoned that because the prioritized item was held in a state susceptible to rTMS, its disruption may have had the effect of reducing the competitive inhibition that it placed on the unprioritized item, which could then be recalled with increased precision. Such an explanation is supported by results from Pertzov et al. (2013), in which retrocues protected prioritized items from competition by unprioritized items. In sum, studies such as these provide a simple, but effective, demonstration that not all items in WM are held in the same state, in keeping with state-based models of WM. Further, these results support the sensory recruitment model of WM, in that visual items (directions of motion) in a prioritized state rely on early visual areas (MT+) for their retention.

The role of speech processing areas (and speech processing mechanisms?) in verbal WM

According to one influential model (Baddeley, 2007), WM for speech sounds depends on a specialized storage buffer—the phonological loop—that is independent from the systems responsible for language production and comprehension. Acheson et al. (2011) used rTMS to test an alternative account whereby this component of Baddeley's model is, in fact, the same mechanism that is also used to carry out the operation of phonological encoding—specifying the speech sounds corresponding to the words to be spoken in an utterance (Acheson and MacDonald, 2009). To test this, they first scanned their subjects with fMRI to identify regions of the left hemisphere activated by two discrete stages in the speech production cascade: lexical retrieval (operationalized with a picture-naming task) and phonological retrieval (operationalized with a paced nonword reading task). In a separate rTMS session, subjects again performed picture naming and nonword reading plus a test of verbal WM for nonwords. For each task, 10-Hz rTMS was tailored to target the cognitive process of interest: four pulses from –100 to +300 ms relative to picture onset; thirty

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pulses during the 3 seconds when the final of three five-nonword chains was displayed for reading; and thirty pulses during the 3-second delay period separating the presentation and recall of nonwords. Critically, subjects performed these three tasks twice—once while rTMS targeted the mid-middle temporal gyrus (mMTG; identified with fMRI of picture naming) and once while rTMS targeted the posterior superior temporal gyrus (pSTG; identified with fMRI of nonword reading). The result produced a double dissociation, with rTMS of the mMTG affecting the picture-naming performance, but not the two nonword tasks, and rTMS of the pSTG affecting the two nonword tasks, but not picture naming.

Conclusion from "virtual lesion" studies

In summary, these "virtual lesion" studies provide evidence that is generally consistent with sensorimotor recruitment and state-dependent models of WM. rTMS of the PFC and SPL disrupts manipulation of the contents of WM. Online TMS and rTMS of the PFC disrupt the control of behavior guided by the contents of WM (i.e., recognition and recall responses), but not the delay-period retention of this information. The opposite is true for the SPL. Regions associated with the perceptual analysis of sensory information (e.g., primary somatosensory and primary visual cortex) or with the preparation of complex motor output (pSTG for speech production) are critical for the delay-period retention of to-be-remembered information. Finally, the dependence of the effects of TMS on the priority status of information provides evidence for state-dependent models of WM.

The "perturb-and-measure" approach

The "perturb-and-measure" approach using TMS is one of the more challenging ways in which to apply TMS. It is, however, also very powerful, as it can reveal the physiological consequences of the effect of TMS on behavior. Perturb-and-measure was first described by Paus (2005), in which TMS was delivered during positron emission tomography (PET) scanning in order to infer causal interactions within distributed brain networks. Early work combining TMS with EEG (Ilmoniemi et al., 1997), PET (e.g., Paus et al., 1997), and fMRI (Bohning et al., 1998) applied stimulation during rest and showed the immediate propagation of TMS-evoked activity, both at the targeted region and at regions distal to the stimulation site.

The ability of TMS to produce a physiological perturbation of brain activity was therefore revealed to be an effective means of assessing the influence of a targeted brain region on the rest of the brain; this approach could also be applied during the performance of behavioral tasks to show functional networks engaged in support of specific mental processes (Driver et al., 2009; Johnson et al., 2012; Ruff et al., 2009). Further, with an appropriate experimental design, the psychological mechanisms supporting distinct mental processes can also be probed with this approach (Bestmann and Feredoes, 2013), as can the effects of cognitive training (Kundu et al., 2013) and even the state of otherwise "hidden" mental representations (Widhalm and Rose, 2019).

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Effects produced by the perturb-and-measure approach should be considered distinct from the disruptive and/or compensatory activity produced by the virtual lesion approach described above, in that the logic is not to affect task behavior, but instead to assess effective connectivity via the propagation of activity through an anatomical network (Bestmann and Feredoes, 2013).

One such study (Johnson et al., 2012) addressed the simple question of how cortical responsiveness to TMS differs during the delay period of a spatial WM task vs during a perceptually identical fixation task. For the memory task, observers were instructed to remember the locations of four objects presented sequentially at different screen locations. During the subsequent delay period, two TMS pulses were delivered to the left SPL 750 ms and 2750 ms after the offset of the final memory item. For the fixation task, participants simply fixated a small cross at the center of the screen while single pulses of TMS were delivered to the SPL at 2-second intervals. In each case, EEG was recorded and the effect of task performance on the TMS-evoked response was assessed. Results revealed that, when applied during the delay period of the WM task, the amplitude of the TMS-evoked response was larger and the spatial spread of significant TMS-evoked activations to task-relevant cortical areas distal to the site of stimulation (e.g., the FEF) was increased, relative to the fixation condition. This supports a role for inter-area interactions in the storage of spatial locations in WM.

The perturb-and-measure approach can also be used to test models of cognitive operations. For example, a critical role of the DLPFC in preventing distraction by irrelevant stimuli has long been known (see, for example, Chao and Knight, 1998), but the way in which it serves to protect WM contents remains a topic of debate. Two proposed mechanisms are enhancement of relevant information (e.g., Sakai et al., 2002) and suppression of irrelevant information (Clapp et al., 2010). To adjudicate between these two possibilities, Feredoes et al. (2011) applied three TMS pulses at 10 Hz to the right DLPFC during the delay period of a visual WM task, which required memory for either faces or houses. Critically, the timing of TMS coincided with the presentation of distracting stimuli during the delay (house stimuli on face-memory trials and face stimuli on house-memory trials). Face and house stimuli were chosen because their processing is known to depend on activity in distinct regions of the posterior cortex—the fusiform face area (FFA) and the parahippocampal place area (PPA), respectively. Results revealed that the short-pulse train produced a significant increase in BOLD signal in the cortical areas associated with processing of the item currently being stored in WM—the FFA during face memory and the PPA during house memory—with no detectable effect in regions related to distractor representation. These results were taken as causal evidence of a role for the DLPFC in mitigating the disruptive effect of distractors by enhancing the maintenance of relevant information in WM. This study provided a potent demonstration of how concurrent TMS and fMRI can be used to test the predictions of competing theories regarding the mechanisms supporting cognitive functioning—in this case, enhancement of relevant targets vs suppression of irrelevant distractors.

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Another application of the perturb-and-measure approach is as a tool to assay the state of WM representations. A series of studies from our group has used a dual serial retrocuing (DSR) task, together with a multivariate pattern classification analysis (MVPA)[3] of fMRI and EEG, to assess whether items "in WM" can be maintained in different states. The DSR task is a variant of the retrocuing task described above, with the difference being that each trial presents two memory tests—after the first retrocue and the first memory test, a second retrocue indicates which of the two items in WM will be tested by the second memory test. Using this method, Lewis-Peacock and colleagues (LaRocque et al., 2013, 2017; Lewis-Peacock and Postle, 2012) had observed that, after the first retrocue, MVPA evidence for the uncued item (the "unprioritized memory item," UMI) dropped to baseline levels. This was a surprising result, because subjects knew that there was a 50 percent chance that, after the first memory probe, the second retrocue would prioritize the previously uncued item. Furthermore, it was known that the initially uncued item (the UMI) remained "in WM," because on this 50 percent of trials, recognition performance with the initially uncued item was almost as high as it was on the other 50 percent of trials, when recognition of the initially cued item was probed a second time. How then is one to understand that evidence for an active trace of the UMI drops to baseline as though it has been forgotten? In the study that we summarize next, Rose et al. (2016) used single pulses of TMS to find neural evidence that the UMI was indeed maintained in a privileged state, despite the absence of evidence for its active representation in fMRI and EEG data (LaRocque et al., 2013, 2017; Lewis-Peacock et al., 2012).

Rose et al. (2016) first scanned subjects with fMRI while they performed the DSR task, then used MVPA to identify cortical regions involved in the delay-period representation of items from the three stimulus categories—faces, directions of motion, and phonology of printed words. Subsequently, the same subjects performed the task while EEG was recorded and single pulses of TMS were delivered to regions identified by MVPA. The EEG data replicated previous findings, with MVPA evidence for an active representation of the UMI dropping to baseline after the first retrocue. However, the delivery of a pulse of TMS had the effect of briefly reactivating the neural representation of the UMI. Importantly, this effect was specific to the cognitive state, because the TMS-evoked response following the second retrocue did not produce a comparable reactivation of the uncued item, presumably because subjects knew that, after the second retrocue, the uncued item was no longer relevant and so it had been dropped from WM.

To summarize, the perturb-and-measure approach can produce causal evidence that constrains the psychological theory and advances our understanding of the physiology underlying WM processes. While a technically challenging approach, the nature of the evidence it can provide makes it an invaluable tool for bringing together different, normally separate, lines of evidence.

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The neuromodulation approach

The final line of research to be considered here involves the delivery of trains of TMS in an effort to modulate ongoing neural activity. It has long been postulated that WM functions are mediated by oscillatory neural activity in various frequency bands (Jacob et al., 2018; Lisman and Idiart, 1995; Lisman and Jensen, 2013; Roux and Uhlhaas, 2014). For example, Roux and Uhlhaas (2014) have proposed that oscillatory activity in the gamma-band (40–100 Hz) plays a role in the active maintenance of information in WM, whereas activity in the alpha-band (8–12 Hz) reflects the inhibition of task-irrelevant information during maintenance, and activity in the theta-band (4–7 Hz) supports the storage of temporally ordered information. Supporting the latter proposal, a recent study by Jacob and colleagues (2018) demonstrated that theta-band synchrony between the frontal and parietal cortices of nonhuman primates predicted performance on a task requiring short-term maintenance of temporal order information. This correlational finding suggests that increasing theta-band synchrony between these two areas should improve WM performance.

One exogenous means of influencing theta-band synchrony between the frontal and parietal cortices is by applying brief trains of theta-frequency rTMS to bias or entrain activity in the targeted area, or between the targeted area and other areas, to the stimulation frequency (Hanslmayr et al., 2019; Thut et al., 2011). Using this method, Albouy and colleagues (2017) reported rTMS-induced enhancement of theta-band activity and an associated improvement in WM. Specifically, 5-Hz rTMS was applied to the left IPS of the human observers during the delay period of an auditory WM task. Stimulation selectively improved performance in a task requiring the maintenance of temporal order information, but not in a control condition involving melody comparison, nor when 5-Hz arrhythmic stimulation was applied. Additionally, simultaneous EEG recording revealed that 5-Hz rhythmic stimulation increased theta-band synchrony between frontal and parietal sites, which persisted beyond the stimulation interval, and the magnitude of which predicted individual performance improvements on the WM task.

Using a similar approach, Hamidi and colleagues (2009a) used rhythmic rTMS to investigate the role of alpha-band oscillatory activity in the short-term maintenance of spatial information. Recall that a study by this same group (Hamidi et al., 2008, reviewed above) showed that 10-Hz rTMS of the SPL led to faster RTs in a task that required the short-term retention of spatial locations. To clarify the mechanisms supporting this rTMS-induced behavioral facilitation, Hamidi et al. (2009a) applied trains of 10-Hz rTMS to the SPL of healthy observers during the performance of either a spatial or an object WM task, while EEG was recorded. Results revealed that delay-period 10-Hz rTMS produced differing effects on delay-period alpha-band power in different individual participants, with the magnitude and direction of this effect being negatively correlated with its effect on behavior. A TMS-related increase in alpha-band power disrupted performance, whereas a TMS-related decrease improved it. This effect was specific to task (WM for locations, but not for objects) and to rTMS target (SPL, not the PCG cortical control area), and was source-localized to cortical areas implicated in the short-term retention of spatial infor-

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mation, including dorsal stream frontal regions and occipital/parietal regions. What does this finding suggest about the role of alpha-band power in WM? Recall that alpha-band oscillatory activity has been proposed to reflect the functioning of an inhibitory mechanism, which suppresses task-irrelevant visual processing during both perception and WM (Jokisch and Jensen, 2007; Klimesch et al., 2007). Thus, under normal circumstances, alpha-band power would be expected to increase over areas representing task-irrelevant information and to decrease over areas representing information needed for task performance (see discussion of Sauseng et al., 2009 below for evidence of alpha modulations during the delay period of a WM task). In the present case, however, alpha-band activity modulations were artificially induced by rTMS in a *task-relevant* area. According to the hypothesis that alpha activity is associated with suppression of local processing, increasing alpha in this area would be expected to disrupt performance, whereas reducing alpha would improve it. This is what was found, supporting an inhibitory role for alpha-band oscillations during maintenance in WM.

Another study (Sauseng et al., 2009) used rTMS to directly examine the role of alpha-band activity in the suppression of task-irrelevant information during a WM task. In a preliminary EEG study, observers were presented with bilateral arrays consisting of either two or four colored squares, with the instruction to remember the squares on the cued side of the screen and to ignore the items on the uncued side (as in Luck and Vogel, 1997). The number of squares that could be held in WM was closely related to the amplitude of alpha-band activity recorded from the parietal electrodes ipsilateral to the remembered information (i.e., over sites representing the task-irrelevant items). This finding is consistent with the proposed role for alpha-band oscillations in suppressing cortical areas representing potentially distracting, task-irrelevant information. In a second experiment, the authors used rTMS to determine whether the observed relationship between increased ipsilateral alpha-band power and WM capacity reflected more than a simple correlation. Short trains of 10-Hz rTMS were applied to the parietal lobes, either contralateral or ipsilateral to the remembered items, during the retention interval of the color WM task used in the preliminary study. As predicted, ipsilateral rTMS produced an increase in performance, whereas contralateral rTMS produced a decrease, presumably due to its effects on power in the alpha-band.

The research reviewed in this section supports a role for oscillatory neural activity in mediating WM component functions. It is a burgeoning area of WM research and the ability to modulate oscillations via TMS provides a distinct methodological advantage in this area of investigation.

Challenges and future directions

The research reviewed in this chapter highlights the usefulness of TMS for studying the neural and cognitive systems supporting WM. Research using variants of the virtual lesion approach has confirmed and extended findings from neuroimaging and EEG studies, suggesting important, but distinct, roles for both higher-order frontal and parietal cor-

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tices and for primary sensory and motor areas in mediating WM processes. Research using the perturb-and-measure approach has elucidated the neural bases of various WM functions. Finally, research using rhythmic neuromodulatory TMS has begun to elucidate the role of oscillatory dynamics in WM function. Going forward, there are exciting possibilities on the horizon. For example, combining TMS with computational models of WM that predict specific physiological mechanisms (e.g., persistent firing vs activity-silent encoding of information) could be manipulated with modes of TMS aimed at enhancing or inhibiting these mechanisms. TMS can also be used to modulate connections between brain regions, which could be combined with functional and effective connectivity methods to reveal which connections are biologically relevant (see, for example, Nee and D’Esposito, 2016). The ability of TMS to interact with intrinsic oscillations has already been shown to be an effective way to probe the contribution of these oscillations to WM, and there remains much work to be done in this area to fully understand how rhythmic activity carries behavioral information. TMS will undoubtedly form a critical component of such investigations.

Conclusions

Our understanding of WM is rapidly shifting, as more sophisticated techniques reveal the complexity of how information is maintained over the short term. TMS has been instrumental over the last few decades of neuroscientific WM research in testing and refining findings from otherwise correlational techniques and from psychological models. The future is clearly in the combination of TMS with other investigative techniques, along with computational and theoretical models, as a means to provide unique forms of evidence that can help the field progress.

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Notes:

(1) Note that, in this era, specific stimulation sites were identified using a variety of methods that were likely not very precise (for a comparison of different methods of TMS targeting, see Ahdab et al., 2010 For example, in the Mottaghy et al. (2002) study, individual areas were targeted by positioning the coil a fixed distance away from the motor cortex stimulation site that was found to produce the largest motor evoked potentials in each subject. Thus, the mapping of stimulation site to specific brain areas should be viewed as approximate.

(2) Due to a programming error, the frequency of stimulation was 4.7 Hz for some subjects and 4.3 Hz for others.

(3) MVPA refers to methods from machine learning that use patterns of neural responses to decode the information content of neural activity (Haxby, 2012).

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