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Hemisphere-specific parietal contributions to the interplay between working memory and attention

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Abstract

In order to achieve our moment-to-moment goals, we must often keep information temporarily in mind. Yet this working memory (WM) may compete with demands for our attention in the environment. Attentional and working memory functions are thought to operate by similar underlying principles, and they often engage overlapping fronto-parietal brain regions. In a recent fMRI study, bi-lateral parietal cortex BOLD activity displayed an interaction between working memory and visual attention dual-task demands. However, prior studies also suggest that left and right parietal cortices make unique contributions to WM and attentional functions. Moreover, behavioral performance often shows no interaction between concurrent WM and attentional demands. Thus, the scope of reciprocity between WM and attentional functions, as well as the specific contribution that parietal cortex makes to these functions, both remain unresolved. Here, we took a causal approach, targeting brain regions that are implicated in shared processing between WM and visual attention, to better characterize how those regions contribute to behavior. We first examined whether behavioral indices of WM and visual search differentially correlate with left and right parietal dual-task BOLD responses. Then, we delivered transcranial magnetic stimulation (TMS) over fMRI-guided left and right parietal sites during dual-task WM-visual search performance. Only right-parietal TMS influenced visual search behavior, but the stimulation either helped or harmed search depending on the current WM load. Therefore, while the left and right parietal contributions were distinct here, attentional and WM functions were co-dependent. Right parietal cortex seems to hold a privileged role in visual search behavior, consistent with prior findings, but the current results reveal that behavior may be sensitive to the interaction between visual search and WM load only when normal parietal activity is perturbed. The parietal response to heightened WM and attentional demands may therefore serve to protect against dual-task interference.

The working memory (WM) process of maintaining information temporarily in mind, in the absence of external input, has been described as internally-oriented attention (Chun, 2011; Kiyonaga & Egner, 2013). Attentional and working memory processes are thought to rely

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on many of the same neural functions (Awh & Jonides, 2001; Gazzaley & Nobre, 2012) and demands on one domain can impact the other (Barrouillet et al., 2011; Fockert et al., 2001; Kiyonaga & Egner, 2014a, 2014b; Watanabe & Funahashi, 2014; Woodman & Luck, 2010; Zokaei et al., 2014). Likewise, in a recent fMRI study we observed an interaction in the fronto-parietal response between dual-task visual WM and attentional demands. Namely, visual search-related BOLD effects were magnified when the concurrent WM load was greater (Kiyonaga et al., 2017). Behavioral measures of WM and visual search dual-task performance were also anti-correlated, corroborating theories of a competitive trade-off between these task demands.

Despite a great deal of evidence for reciprocity between WM and attention oriented toward external stimuli, however, there is a clear conceptual distinction between them: unlike the object of externally-oriented attention, WM content must be endogenously maintained when the sensory input is no longer present to evoke the representation. Accordingly, recent work has highlighted important distinctions in the mechanisms underlying WM vs. attention, and cautions against conflating the two concepts (Bae & Luck, 2018; Ester et al., 2009; Harrison & Bays, 2018; Mendoza-Halliday & Martinez-Trujillo, 2017; Myers et al., 2017; Sheremata et al., 2018; van Kerkoerle et al., 2017). Indeed, concurrent demands on either visual WM or attention sometimes fail to impact behavior in the other domain (Hollingworth & Maxcey-Richard, 2012; Woodman et al., 2001). Such null effects support the idea that WM and attentional processes may be independent, further undermining the prospect of their reliance on identical neural substrates. There is little consensus as to why WM and (externally-oriented) attention demands influence each other in some cases but not others, or what neural functions underpin the relationship between the demands (*cf.* Lorenc et al., 2021; Oberauer, 2019).

A variety of WM- and attention-related demands are associated with activity in distributed fronto-parietal regions (Christophel et al., 2017; Corbetta & Shulman, 2002; D'Esposito & Postle, 2015; Eriksson et al., 2015), and regions of the parietal cortex are thought to uniquely serve as a bottleneck for attention and WM capacity (Marois & Ivanoff, 2005; Xu & Chun, 2009). Indeed, many causal studies implicate parietal cortex as a substrate for WM and attentional functions (Beck et al., 2006; Berryhill et al., 2011; Chouinard et al., 2017; Emrich et al., 2016; Husain et al., 2001; Juan et al., 2017; Koenigs et al., 2009; Luber et al., 2007; Mackey & Curtis, 2017; Mackey et al., 2016; Morgan et al., 2013; Oliveri et al., 2001; Schenkluhn et al., 2008). However, these studies have targeted a range of parietal subregions, and consequently attribute a variety of distinct sub-functions to parietal cortex. It remains unclear which subregions are necessary for both WM and attentional function.

Parietal cortex is functionally diverse (Duncan, 2010) and can be parcellated into many subdivisions (Capotosto et al., 2013; Cavada & Goldman-Rakic, 2004; Vincent et al., 2008; Yeo et al., 2015). Thus, different parietal regions may play unique roles in WM and attentional processing. Moreover, using transcranial magnetic stimulation (TMS), left- and right-hemisphere parietal cortex have been shown to play distinct attentional roles (Mevorach et al., 2006), and make dissociable contributions to cognitive control over WM content (Kiyonaga et al., 2014). For instance, an offline TMS study shows that a left parietal region strengthens the effect of WM content to guide attention toward matching visual

targets. The same study shows that a right parietal region suppresses the effect of irrelevant visual distraction instead (Kiyonaga et al., 2014). Thus, while bi-lateral parietal regions are engaged by WM and visual attention demands, the functions could potentially be insulated from cross-competition via hemispheric lateralization. Both neuroimaging and lesion data also suggest hemispheric specialization for verbal WM vs. visuo-spatial processing in left vs. right parietal cortex, respectively (de Schotten et al., 2011; D'Esposito et al., 2006; Smith et al., 1996). However, those observed distinctions may depend primarily on the content domain (i.e., verbal vs. spatial), or be mainly quantitative differences (vs. qualitative; Rushworth et al., 2001), as opposed to distinguishing between WM and attention functions, per se.

While evidence for lateralization of WM vs. attentional function is mixed, parietal lesion and TMS studies reliably demonstrate that each hemisphere preferentially processes stimuli from the contralateral visual hemifield (Blankenburg et al., 2010; Hamidi et al., 2008; Hilgetag et al., 2001; Mackey et al., 2016; Sauseng et al., 2009; Walsh et al., 1998; Wolinski et al., 2018). For instance, alpha frequency parietal stimulation (10Hz) can impair WM for contralaterally-presented visual stimuli while showing the opposite effect for ipsilateral stimuli (Sauseng et al., 2009). Similarly, TMS to the right temporoparietal junction can increase attentional capture by distractors in the left visual hemifield, while having the opposite effect on right-lateralized stimuli (Chang et al., 2013). During a visual attention task, therefore, we would expect parietal stimulation to differentially impact attentional processing in the contra- and ipsilateral visual hemifields. However, it is unclear how this hemifield-specific impact would interact with concurrent WM and attentional load, when fMRI findings suggest that both hemispheres would be engaged.

In sum, reciprocity between WM and attentional functions is inconsistent across studies. Fronto-parietal regions are associated with a variety of WM- and attention-related processes, but it is unclear what specific functions are reflected by activations in these regions, or whether those functions are shared between WM and attentional domains. The parietal cortex is considered especially important to WM and attentional processes, but causal studies provisionally indicate that the two domains of processing may be differentiated across the two cerebral hemispheres. Even causal lesion and offline TMS approaches are temporally non-specific, leaving ambiguity about which task stages rely on the studied region, especially in complex dual-task conditions that comprise several sub-processes. The current study aimed to address these ambiguities.

Here, we tested the temporally-specific causal contributions of parietal regions to WM, visual attention, and the interaction between them. We examined whether regions that display similar fMRI responses, in a dual-task WM-visual search context, play unique functional roles in performance. We first conducted new analyses on our previous data set to correlate left and right parietal fMRI responses with behavioral indices of WM and visual search performance. We then used online, event-locked TMS to test whether these correlative fMRI observations translate into a causal role in behavior. We stimulated left- and right-hemisphere parietal regions to examine the effect on the interplay between WM and attentional demands. Previous findings suggest that left parietal cortex may preferentially support WM maintenance processes, while right parietal cortex may

preferentially support visual search efficiency (Kiyonaga et al., 2014). Here we causally tested this idea by delivering TMS, time-locked to visual search performance, at varying levels of concurrent WM load and visual search difficulty.

Materials and Methods

Study overview

We first re-analyzed fMRI data from a previous study (Kiyonaga et al., 2017) to examine whether left and right parietal responses correlate with behavioral performance in a WM-attention dual-task setting. We then targeted group activation peaks from the previous study to causally manipulate the implicated parietal regions in a new cohort. For the TMS study, high-resolution T1-weighted anatomical brain scans were first acquired for stereotaxic neuronavigation to TMS targets. Left and right parietal group coordinates were mapped onto individual anatomical images as experimental TMS targets. During a separate experimental session, short trains of online TMS (5 pulses at 10Hz) were applied during a dual WM-visual search task (Figure 1), to each of three scalp locations. Left parietal, right parietal, and vertex sites were each targeted for stimulation in separate experimental blocks, in counterbalanced order. The vertex control site was employed to reproduce the sensations of TMS to the active sites of interest, and to account for non-specific effects of the stimulation (Pitcher et al., 2008). Participants were first trained on the WM-visual search dual-task procedure, which was modeled closely after the task described in a recent paper (Kiyonaga et al., 2017). Participants then completed experimental blocks of the task, while TMS was delivered online during the WM delay of each trial.

TMS study participants and approvals

Effect sizes for TMS main effects and interactions across a variety of WM studies fall in the range of $\eta_p^2 = 0.21$ to 0.44, with a mean of 0.32 (Beck et al., 2006; Heinen et al., 2017; Lee & D'Esposito, 2012; Morgan et al., 2013; Sauseng et al., 2009). With the expectation of an effect size in the middle of this range ($\eta_p^2 = .32$), the G*Power 3.1.9.2 (http://www.gpower.hhu.de) tool for *a priori* calculation of required sample size for repeated-measures ANOVAs indicates that a sample of n = 15 would yield an actual power of .87 at $\alpha = .05$. Here, 17 healthy volunteers from the community were screened for TMS contraindications and gave written informed consent to participate. All procedures were carried out in accordance with the experimental protocols that were approved by the Duke University Institutional Review Board. As per the stipulations of these protocols, individual subject data will be made available upon request, but all experimental code and group summary data will be available at https://osf.io/h8gtv/. Unthresholded group fMRI maps are available at http://neurovault.org/collections/AZELKTWQ/.

Volunteers were recruited from a pool of the laboratory's previous research participants for whom recent high-resolution T1-weighted brain scans were available. All participants were paid $20 per hour for their participation. Three participants were excluded for poor task performance (< 55% accuracy) on either the WM (2 participants) or visual search task components (1 participant). Therefore 14 participants were included in the final TMS analysis (7 male; mean age: 29; age range 19-43).

Dual-task WM/Visual Search Procedure

The task was designed to independently vary WM and visual attentional load in a fully balanced 2 (WM load: 1 vs. 2 items) × 2 (visual search difficulty: easy vs. hard) factorial design. The task comprised a delayed match-to-sample WM test, with a visual search during the delay (Figure 1a). Across different trials, participants had to remember either one (low WM load) or two (high WM load) images of faces or houses for a later memory probe (Figure 1b). During the WM delay, participants performed a visual search for a perfectly vertical target stimulus among horizontal (easy search) or diagonally tilted (hard search) distractors (Figure 1b). TMS was delivered at the onset of the visual search display, during the WM delay, for all trials (Figure 1a). Because our TMS targets were motivated by BOLD activations during visual search performance (Kiyonaga et al., 2017), we applied TMS during the comparable epoch of the current task. This online TMS protocol is expected to have a short-lived impact on neural activity and would thus be unlikely to last the duration of the trial. Our goal was to examine the roles of the targeted parietal regions in visual attention performance (when the TMS should have its effect) as a function of concurrent WM maintenance demands.

The task was programmed and presented in Matlab (Mathworks Inc., Natick, MA) using the Psychophysics Toolbox extensions (Brainard, 1997). Face stimuli were 144 trial unique grayscale images of male and female faces, drawn from several databases (Endl et al., 1998; Kanade et al., 2000; Lundqvist et al., 1998; Minear & Park, 2004; Oosterhof & Todorov, 2008; Tottenham et al., 2009), and cropped to include only the "eye and mouth" region. House stimuli were 144 trial unique grayscale exterior images drawn from local real estate websites. Visual search stimuli were 16 male and female bodies, with heads cropped (Downing et al., 2001), and 16 tools (hammers and wrenches) drawn from freely available online sources. Stimuli were displayed against a neutral grey background.

Each trial began with a variable inter-trial interval (1-4 sec), designed to jitter the delay between successive TMS trains. The WM sample then appeared for 2 sec. Low load WM samples consisted of a single, centrally-presented face or house. High load WM samples consisted of either two faces or two houses presented side-by-side. After a 2 sec fixation delay, a visual search display appeared for 1 sec. Each search array comprised four stimuli (either all tool or all body images) at the corners of an imaginary square. In all conditions, the target stimulus was perfectly vertical, while three distractors were tilted to the left or right. The task was to indicate whether the target stimulus was oriented right-side up or upside down. Participants entered visual search responses with a right-handed keyboard button press of either "I" (right-side up) or "J" (upside-down). For easy search trials, the distractors were perfectly horizontal (i.e., tilted 90° to the left or right), making them easily discriminable from the vertical target. For hard search trials, on the other hand, distractors were slanted 45° to the left or right, making their orientation less discriminable from the vertical target (Treisman & Gelade, 1980).

The type and number of stimuli were identical for easy and hard searches, equating the amount of perceptual input across all conditions. Only the orientation difference between the target and distractor stimuli varied, serving as the manipulation of search difficulty. The search target locations were counterbalanced and were thus equally likely to appear on the

left or right side of the array in all conditions. The TMS train coincided with the onset of the visual search display, and lasted 500 msec (i.e., 5 pulses delivered at 10Hz frequency). The 1 sec search display was followed by a 500 msec delay during which visual search responses could still be entered, for a total response window of 1.5 sec. Then a WM probe image, which was either a novel image (50% of trials) or an exact match to a WM sample, appeared for 3 sec. Participants made left-handed keyboard button press to indicate whether the image was the same or different from any item in the WM sample set. Participants were instructed to maintain central fixation throughout the trial.

WM samples were chosen in random order and never repeated across the experiment, except as matching probes. Visual search stimuli, locations, and orientations were also chosen in random order on every trial but could repeat across trials. Participants completed one practice block of 16 trials prior to any stimulation, and then three experimental runs wherein stimulation was delivered during the WM delay. Every run—one for each TMS target site— lasted ~15 minutes and comprised 5 blocks of 16 trials each, for a total of 80 trials in each TMS target condition.

Kiyonaga et al. (2017) reanalysis

In a previous study, we measured fMRI activity during a dual-task WM and visual attention paradigm. All details of the fMRI acquisition and analysis are reported in Kiyonaga et al., 2017, and the relevant analyses are summarized below. The original task procedure closely resembled the paradigm described above for the current TMS follow-up (Figure 1a). The task comprised a WM delayed match-to-sample, wherein a visual search was completed during the WM delay. The primary difference in the original study task was that the visual search component consisted of a series of four search trials, lasting 8 sec in total, rather than just a single search. The new fMRI analyses focus on this search epoch.

A model of the task was created for each subject via vectors corresponding to the onset of the visual search series (8 s boxcar) for each condition. The model included regressors for WM and visual search load and stimulus category, resulting in a total of 16 regressors of interest. Analyses collapsed across stimulus category, however, producing four main conditions of interest—Low WM/Easy Search, Low WM/Hard Search, High WM/Easy Search, High WM/Hard Search. WM sample and probe epochs, error trials, head-motion parameters, and grand means of each run were modeled as nuisance regressors. Single-subject contrasts were calculated to establish the hemodynamic correlates of working memory load, visual search difficulty, and their interaction effects. Group effects were assessed by submitting the individual statistical parametric maps to 1-sample t-tests where subjects were treated as random-effects. To control for false-positives we applied a whole-brain voxel-wise FDR-correction ($p < .05$, combined with a cluster extent of 20 voxels).

During the delay-spanning visual search task epoch, we observed an interaction between factors of WM load (1 vs. 2 items) and visual search difficulty (easy vs. hard) at the whole-brain level. This interaction contrast revealed both left and right parietal clusters of activity that were sensitive to the combination of task demands (Figure 2; Figure 3b in Kiyonaga et al., 2017; unthresholded t-map available at http://neurovault.org/collections/AZELKTWQ/). The effect of visual search difficulty was amplified when concurrent WM load was higher.

While there was no corresponding interaction between factors in behavior, there was a strong negative correlation between WM accuracy and visual search RT measures across participants (Figure 2e in Kiyonaga et al., 2017). This correlation—better WM being associated with slower difficult visual search—suggests a possible tradeoff between task components. That is, in this dual-task behavior, the interplay between WM and visual search manifested as a negative relationship between the different tasks, rather than a within-task interaction between factors. We reasoned that these basic task performance measures—that traded off with one another—might also relate to the BOLD interaction response during this task. We were also further motivated by previous evidence for a distinction between left and right parietal regions in WM and attentional function; we therefore examined whether beta estimates from left and right parietal clusters differentially related to WM recognition and visual search performance measures.

Using MarsBaR software (http://marsbar.sourceforge.net), 6 mm spherical ROIs were centered on peak group activations from the left and right parietal clusters that displayed an interaction. Mean β estimates were extracted from the ROIs for every participant (n = 28) in each of the four primary task conditions. A double subtraction between the effects of WM load and visual search difficulty was calculated to characterize the strength of the interaction in BOLD activity for each participant. A larger interaction effect indicates that the visual search difficulty effect was more strongly modulated by the concurrent WM load. That neural interaction metric was then correlated with individual measures of mean WM probe recognition accuracy and visual search RT. We also conducted control correlation analyses including WM probe RT and visual search accuracy, although we had no a priori hypothesis that those measures should be related to the neural interaction metric here. We conducted these analyses to rule out the possibility that any dissociation between the ROIs might be driven by their relationships to a given type of performance data (i.e., accuracy vs. RT), rather than cognitive task demand (i.e., WM vs. visual search).

TMS methods

Target Selection—Stimulation targets were based on group activation coordinates from the recent study described above (Kiyonaga et al., 2017). Previous studies have indicated that there may be functional distinctions between left and right posterior parietal cortex in WM and attentional processes (Beck et al., 2006; Mevorach et al., 2006; Yamanaka et al., 2010), and specifically in the interplay between those processes (Kiyonaga et al., 2014). Brain-behavior correlations, furthermore, showed dissociable relationships for left vs. right parietal clusters with WM and search behavior (described below; Figure 2). We therefore identified peaks within left and right parietal clusters of the interaction contrast and designated them as TMS targets, to test the causal roles of these regions in dual-task WM-visual search performance. Both clusters spanned large sections of the parietal cortex, so we constrained our targets to sites that were among the top 3 local maxima for the interaction contrast and displayed similar *t*-values to each other. An alternative approach would have been to select symmetrical sites in each hemisphere, but we wanted to maximize the likelihood that the targeted experimental regions would be engaged by the task to similar degrees. The left hemisphere target was MNI −36 −46 55, along the anterior portion of the intraparietal sulcus, and the right hemisphere target was MNI 33 −64 61, on the middle

portion of the superior parietal lobule (Figure 2). Each individual's vertex was measured as the point midway between the nasion and the inion (at x = 0).

TMS equipment—The Brainsight 2 frameless stereotaxic neuronavigation system (Rogue Research, Montreal, Canada) was used to 1) co-register an MNI brain to each participant's anatomical MRI, 2) localize the TMS targets and corresponding scalp position of the TMS coil for each participant, and 3) monitor the coil position and record all TMS pulse trajectories throughout each stimulation run. Stimulation was delivered with a Magstim Rapid[2] stimulator via a Magstim Double 70mm Air Film Coil. In light of evidence that motor threshold is an unreliable index of the excitability of other brain regions (McConnell et al., 2001; Rushworth et al., 2001; Stewart et al., 2001), and in keeping with parameters used in many similar studies (Pitcher et al., 2007, 2008; Silvanto et al., 2008), stimulation was delivered at a fixed intensity for all participants (50% of maximum stimulator output).

Stimulation procedure—Participants were seated in a reclining chair outfitted with a supportive neck rest and adjustable arms to stabilize the coil throughout the sessions (Rogue Research). A laptop was used to present the experimental task and trigger the stimulator. The laptop was positioned on an adjustable tray table and tailored to a viewing distance of approximately 80cm for each participant. Many prior repetitive TMS studies have used offline stimulation to produce temporary reductions in cortical excitability prior to task execution (Parkin et al., 2015), but this method can influence all stages of task processing, and therefore prevents causal inference about the stimulated brain regions in any particular task sub-process. Our TMS targets were selected based on group activation peaks during WM delay-spanning visual search performance. We therefore applied short-lasting trains of online TMS during this visual search epoch of the current task paradigm. Previous studies have successfully used 10Hz stimulation online to perturb neural activity and influence behavior (Beck et al., 2006; Feredoes et al., 2007; Hamidi et al., 2008; Kennerley et al., 2004; Sauseng et al., 2009). We therefore delivered trains of 5 TMS pulses at 10Hz frequency—lasting 500 msec—at the onset of each visual search display (Figure 1a).

Results

Brain-behavior correlation

In the new analysis of the previous study data, BOLD activity measured during the delay-spanning visual search task correlated with individual task performance. However, BOLD responses in left and right parietal regions displayed dissociable correlations with WM and visual search behavior (Figure 2). The interaction in BOLD activity—from the period during visual search performance—manifested as a stronger effect of visual search difficulty when WM load was also high. The magnitude of this interaction effect in the left parietal cluster correlated negatively with WM probe accuracy ($r = -.41$, $p = .029$, 95% CI [$-.68$, $-.048$]), but did not relate to search RT ($r = .17$, $p = .39$, 95% CI [$-.22$, $.51$]). Conversely, the interaction effect in the right parietal cluster correlated negatively with visual search RT ($r = -.40$, $p = .033$, 95% CI [$-.68$, $-.037$]), but did not relate to WM probe accuracy ($r = -.05$, $p = .80$, 95% CI [$-.42$, $.33$]). That is, greater modulation of left parietal activity by WM load related to worse WM performance, while greater modulation of right parietal activity

by WM load related to better visual attentional performance. Fisher's *z*-tests confirmed that the correlations with WM accuracy significantly differed between left and right parietal BOLD response, $z = 1.79$, $p = .037$. Similarly, the correlations with visual search RT also significantly differed between left and right parietal BOLD response, $z = -2.77$, $p = .003$. This suggests that these parietal regions may make unique contributions to dual-task WM and visual search behavior, and that the internally- vs. externally-oriented aspects of behavior may depend on unique neural substrates.

Control analyses further indicated that neither visual search accuracy nor WM probe RT correlated with the BOLD interaction from either parietal site (search accuracy – left parietal, $r = .022$, $p = .91$; search accuracy – right parietal, $r = .29$, $p = .14$; WM probe RT – left parietal, $r = .24$, $p = .21$; WM probe RT – right parietal, $r = .028$, $p = .89$).

TMS-behavior causation

WM probe performance—When TMS was delivered during task performance, WM accuracy averaged 83% correct, confirming that participants followed instructions and were able to complete the task. In a stimulation site (vertex, left parietal, right parietal) × WM load (1 item vs. 2 items) × visual search difficulty (easy vs. hard) ANOVA, WM accuracy was impacted by a main effect of WM load, $F(1, 13) = 65.98$, $p < .001$, $\eta_p^2 = .84$, as well as a marginal main effect of stimulation site, $F(2, 26) = 2.95$, $p = .070$, $\eta_p^2 = .19$, but no other effects of task condition or interactions between factors (all $p > .2$). Memory was less accurate for 2 items (vs. only 1), as expected, and was slightly worse than control after right hemisphere stimulation (Table 1). WM probe RT (for correct responses) was also impacted by a main effect of WM load, $F(1, 13) = 105.37$, $p < .001$, $\eta_p^2 = .89$, as well as a marginal main effect of visual search difficulty, $F(1, 13) = 3.54$, $p = .082$ $\eta_p^2 = .21$, but no effects of stimulation site or interactions between factors (all $p > .14$). Replicating previous findings, WM probe RT was faster when WM load was lower.

Visual Search performance—Because online TMS was delivered at the time of the delay-spanning visual search trial, and was expected to have only a brief impact on neural activity, our analyses focus primarily on visual search performance. Search accuracy was high (mean: 97%, std. dev.: 2.9%), and was unaffected by any task or stimulation conditions (all $p > .1$). To establish that vertex stimulation served as a valid control condition, we first submitted accurate visual search response times (RT) during the vertex TMS condition to a WM load × visual search difficulty ANOVA. As expected, search was slower when targets were less discriminable from distractors (hard search), $F(1, 13) = 67.25$, $p < .001$, $\eta_p^2 = .84$ (Figure 3a). Search was descriptively (but not significantly) slower during higher WM load trials, and there was no interaction between WM and search factors (both $p > .3$). This performance pattern replicates previous findings (Kiyonaga et al., 2017), indicating that the vertex condition is an appropriate control against which to compare performance after experimental TMS.

The influence of parietal TMS during visual attention and WM depends on the visual hemifield of the relevant information (Blankenburg et al., 2010; Hamidi et al., 2008; Hilgetag et al., 2001; Sauseng et al., 2009; Walsh et al., 1998). The omnibus repeated

measures ANOVA therefore included a factor of search target visual hemifield. This produced a $3 \times 2 \times 2 \times 2$ design including stimulation site (vertex vs. left parietal vs. right parietal), target hemi-field (left vs. right), WM load (1 item vs. 2 items), and visual search difficulty (easy vs. hard). The ANOVA revealed a main effect of search difficulty, $F(1, 13) = 69.9$, $p < .001$, $\eta_p^2 = .84$, whereby search was slower in the hard condition. Crucially, the analysis also revealed a 4-way stimulation site $\times$ target hemifield $\times$ WM load $\times$ visual search difficulty interaction, $F(1,13) = 3.7$, $p = .039$, $\eta_p^2 = .22$, which we decompose below (Figure 3b, depicting effect only for search targets contralateral to TMS site). There were no other significant main effects or interactions (all $p > .1$).

To simplify the analyses and display, the remaining results will be examined as a difference from control performance (i.e., RT during experimental TMS – vertex TMS). To parse the significant 4-way interaction, we therefore then ran separate $2 \times 2 \times 2$ ANOVAs for each parietal stimulation site (using the difference score from vertex), including the factors of target hemifield, WM load, and visual search difficulty. Analysis of the left parietal stimulation site condition produced no significant main effects or interactions (all $p > .16$). However, the right parietal stimulation site condition revealed a 3-way interaction between all factors, $F(1,13) = 8.1$, $p = .014$, $\eta_p^2 = .38$. There were no other main effects or interactions (all $p > .13$). The effects of TMS that produce an interaction between task conditions, therefore, seem to be driven by the right parietal stimulation site (however, we display results for both sites for comparison, Figure 3b). Note that because these analyses were performed on difference scores (subtracted from the control TMS condition), it is unsurprising that there are no main effects of search difficulty.

Because of the expectation that parietal TMS may uniquely impact processing in the contralateral visual hemifield, we further decomposed this 3-way interaction with separate 2×2 ANOVAs for each target hemifield, including WM load and visual search difficulty factors (for the right parietal stimulation condition only). While visual search performance was unaffected for targets that were ipsilateral to the stimulation site (no main effects or interaction, all $p > .11$), search for contralateral targets showed a significant WM load $\times$ visual search difficulty interaction, $F(1,13) = 7.8$, $p = .015$, $\eta_p^2 = .37$ (Figure 3b). This finding confirms that the effects of right parietal TMS were specific to processing in the contralateral visual hemifield (and thus results are displayed only for contralateral target conditions).

While there were essentially no differences from control performance on easy search trials, the effect on hard search trials was modulated by concurrent WM load (Figure 3b). Right parietal TMS caused a slowing in search performance relative to control when WM demands were low, but a speeding when demands were highest, and these conditions were significantly different from each other $t(13) = 2.9$, $p = .013$, Cohen's d = .77, 95% CI [25.9, 182.2]. That is, TMS impaired visual attentional performance when only one item was maintained in WM, but improved performance when two items were maintained (10 out of 14 participants show this effect). Therefore, the targeted parietal region is causally involved in dual-task visual search processes, and its involvement varies with current WM maintenance demands. Just as WM load modulates the visual search-related BOLD response in parietal cortex, it also modulates the impact of parietal TMS on search performance.

Discussion

Here we examined whether left and right parietal regions make unique contributions to behavior in a dual-task WM-visual search setting. We first found that the BOLD response in these regions displayed dissociable correlations with basic WM and visual search performance measures: left parietal responses related uniquely to WM probe recognition accuracy and right parietal responses to visual search speed (Figure 2). We then used online TMS to examine whether the correlations reflected a causal role of these regions in behavior. We found that (1) TMS preferentially impacted visual search for targets in the contralateral visual hemifield, (2) mainly right-hemisphere stimulation impacted visual search performance during WM maintenance, and (3) the TMS effect on attentional performance hinged on the level of concurrent WM demand (Figure 3).

Reconciling inconsistent evidence for competition between WM and visual attention

The observed interaction between WM and visual search load factors is consistent with many prior findings that these functions rely on overlapping mechanisms (Awh et al., 1998, 2000; Griffin & Nobre, 2003; Kiyonaga & Egner, 2014b, 2016; Kuo et al., 2009). However, the two demands failed to impact each other behaviorally during the control TMS condition. WM load only modulated search behavior after perturbation of right parietal cortex—a region that has shown a fMRI BOLD interaction during a similar dual-task demand. This study therefore provides causal evidence that the interaction between WM and search demand factors in BOLD activity (Kiyonaga et al., 2017) may reflect control processes that mitigate the impact between concurrent demands to promote successful performance. Cases where such WM and attentional demands fail to influence each other behaviorally are often taken as evidence that WM and attentional rely on distinct processes (Hollingworth & Maxcey-Richard, 2012; Woodman et al., 2001; Woodman & Luck, 2010). However, the current findings suggest that such null behavioral interactions may actually be accompanied by heightened engagement of cognitive control circuitry. Control processes can minimize the competition between functions and eliminate an observable impact on behavior. Behavioral signatures of the interference between WM and attentional functions may therefore only emerge when the cognitive control system is unable to handle the competition between the two—either because the demands are too great or because normal neural activity has been perturbed.

Neural mechanisms of 10 Hz online TMS

The 10Hz online TMS protocol that was delivered here has been used to disrupt behavior, but recent applications of rhythmic stimulation—either sensory or transcranial—indicate that such a protocol might also entrain neural oscillations in the alpha frequency (Graaf et al., 2013; Herring et al., 2015; Mathewson et al., 2012; Sauseng et al., 2009; Spaak et al., 2014; Thut et al., 2011). Parietal transcranial direct current stimulation has further been shown to modulate alpha power and WM capacity (Hsu et al., 2014). This entrainment may be helpful or harmful to behavior, depending on the task goals and the endogenous rhythms of the stimulated region (Riddle et al., 2020). Power in the alpha band, for instance, is increased contralateral to irrelevant distractors and decreased ipsilateral to relevant targets; entrainment of this frequency can likewise impair processing of relevant contralateral stimuli

while improving inhibition of irrelevant distractors (Sauseng et al., 2009). Here, we found that right parietal TMS impaired visual search when WM demands were low, but improved performance when WM demands were high. This finding is broadly consistent with many observations that the pre-stimulation cortical state can determine the direction of TMS effects (Silvanto et al., 2008; Silvanto & Pascual-Leone, 2008). The present finding suggests that WM load modulated the underlying state of the right parietal TMS site, thereby modulating the direction of the TMS effect on behavior. Likewise, although the right parietal BOLD response was (descriptively) modulated more by WM load during the easier visual search condition, here the TMS impact was observed only in the harder visual search condition. This is likely because the region was overall engaged more during the harder search condition, and therefore more receptive to stimulation.

Stimulation (and possibly alpha entrainment) of the right parietal region could have improved discrimination between targets and distractors when demands were highest, when the stimulated region was likely maximally engaged (according to the fMRI findings). Alternatively, stimulation may have interfered with endogenous alpha rhythms, thereby releasing contralateral targets from alpha suppression and improving performance. We can make complementary interpretations to explain the impairment during low WM load: alpha entrainment could have evoked detrimental suppression of contralateral targets, or alpha 'interference' could have disrupted fragile target discrimination processes. It is difficult to distinguish between these possibilities without simultaneous recordings of electrophysiological activity. Regardless of the particular oscillatory mechanism, however, the findings reinforce previous evidence that right parietal cortex plays a preferential role in distractor inhibition (Kiyonaga et al., 2014). The present TMS findings add, however, that concurrent WM load modulates the neural substrates of such visuo-spatial processing. In addition to testing the causal contribution of these parietal regions to behavior, therefore, the transcranial stimulation may serve as something of a probe into the condition-dependent state of the targeted site (Rose et al., 2016).

Functional diversity of parietal cortex

The prior fMRI findings suggest that the targeted parietal regions might also be engaged to overall different degrees during the current experimental task (Figure 2). For instance, while both left- and right-hemisphere ROIs showed interaction effects of comparable magnitude, the left parietal region showed a relatively smaller search difficulty effect during low WM load, as well as overall lower beta estimates than the right parietal target. Thus, the distinct effects of TMS to the two sites could be explained by differing levels of activation at the time of stimulation. This could explain why only right parietal TMS produced a statistically significant change in behavior.

Alternatively, these findings could indicate that the left vs. right parietal regions play diverging functions, and therefore the same cortical effect produces different behavioral outcomes. That is, while both regions display a BOLD interaction of similar magnitude, distinct underlying functional roles may drive the interaction. The left parietal region 1) displays a minimal fMRI effect of visual search difficulty during low WM load, 2) the magnitude of the interaction in this region relates to *worse* overall WM performance, and 3)

stimulation of this region had minimal impact on visual search behavior (and descriptively, the impact occurred only in the easy search condition). The right parietal region, on the other hand, 1) shows a larger fMRI effect of visual search difficulty in both WM conditions, 2) the magnitude of the interaction in this region relates to *better* overall search performance, and 3) stimulation of this region significantly influenced visual search behavior only in the hard search condition. Combined with the tradeoff we have previously observed between WM and visual search measures (Kiyonaga et al., 2017), the fMRI, brain-behavior correlation, and TMS results all converge on the idea that each parietal region may preferentially support a unique aspect of dual-task behavior.

The left parietal TMS target is nearby to a portion of the superior intraparietal sulcus that has been associated with WM capacity (Todd & Marois, 2004; Xu & Chun, 2006), and its engagement may underpin WM storage processes that become taxed when concurrent attentional demands are high. Considering prior findings, the current observations suggest that the interaction in neural response may reflect the region's capacity limit, whereby a stronger interaction relates to worse WM. If the left parietal region underpins WM maintenance, the brief TMS perturbation during visual search may do little harm. Activity in the right parietal region, by contrast, may instead underpin visual attentional efficiency, especially when it is challenged by heightened concurrent load, whereby increased engagement supports better search behavior.

These findings are also consistent with prior evidence for stronger effects of right parietal TMS (vs. left) on WM and attentional function (Beck et al., 2006; Kessels et al., 2000; Yamanaka et al., 2010). These findings may reflect a greater necessity of right parietal regions in these functions, or could be a consequence of the more diffuse attentional scope of the right hemisphere. That is, whereas the left hemisphere is predominantly involved in spatial attention in the contralateral visual hemifield, the attentional scope of the right hemisphere spans both hemifields (Heilman & Van Den Abell, 1980; Mesulam, 1981, 1999). Therefore, the right hemisphere could potentially compensate for TMS to the left hemisphere (when processing right-lateralized stimuli), whereas the left hemisphere is less likely to be involved in processing left-lateralized stimuli.

Caveats and conclusions

While this TMS study provides evidence for unique contributions of the stimulated parietal regions, it does not provide definitive evidence for lateralization of WM and attentional function. We aimed to stimulate regions that would most likely be engaged by the task demands, and thus we targeted sites based on observed functional activations, even though they were not homologous. The left parietal target was located slightly anterior and inferior to the right parietal target. The two regions may thus map onto distinct functional subdivisions of parietal cortex (Yeo et al., 2015), which are associated with distinct patterns of functional and anatomical connectivity (Cavada & Goldman-Rakic, 2004; de Schotten et al., 2011; Vincent et al., 2008). The effects that we observed here could therefore be a result of the differential propagation of the TMS effect throughout a network, wherein a connected region may in fact be the critical causal substrate of behavior. The cortical geometry underneath the TMS coil also likely differed between these targets, and may thus have

influenced the nature and extent of the TMS effect. Moreover, TMS effects were variable across participants, and the modest sample size for the TMS experiment leaves open the possibility that significant effects of left parietal stimulation may emerge with higher power. Nonetheless, these results provide converging correlational and causal evidence that visual WM and attentional demands influence each other, and their interaction is underpinned by parietal cortex activity. However, left and right parietal regions play distinct underlying roles in visual WM and attentional behavior, as TMS perturbation of these regions has distinct and condition-dependent effects on behavior. Left parietal regions may underlie WM maintenance functions, while right parietal regions instead underpin visual search efficiency.

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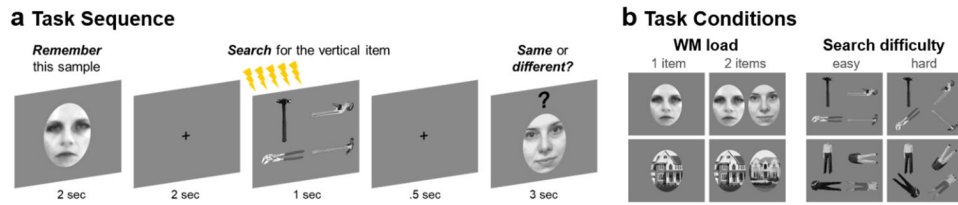
Figure 1. Dual-task design.

a) On each trial, participants remembered 1 or 2 WM sample images, performed a visual search for the single vertical item during the WM delay, and were tested on their WM recognition. A train of 5 TMS pulses was delivered at 10Hz frequency at the onset of each visual search display. b) WM load, for face or house stimuli, was varied between 1 or 2 items. Visual search difficulty, for tool or body stimuli, was varied by making distractors either more or less discriminable from targets.
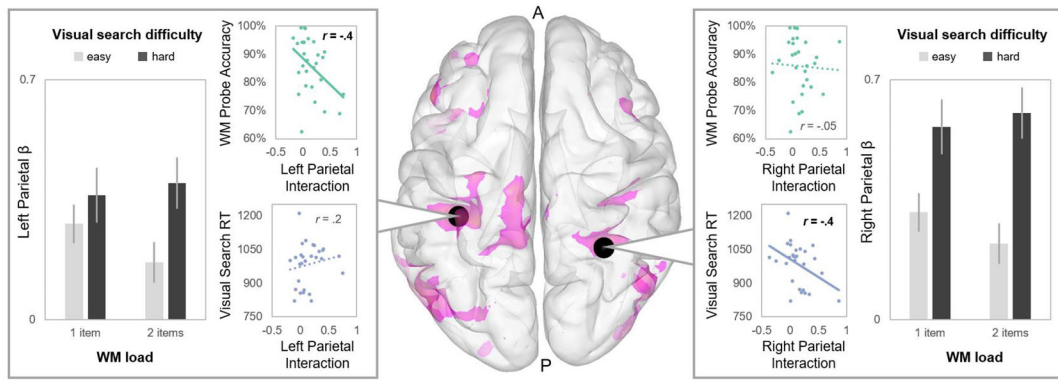
Figure 2. Brain-behavior correlations and TMS targets.
Pink overlay shows regions that exhibited an interaction between WM and visual attentional load (Kiyonaga et al., 2017). Bar graphs show beta estimates extracted from ROIs surrounding local maxima from left and right parietal clusters (peaks marked with black nodes), which served as experimental TMS targets for the current study. Scatterplots show the magnitude of the interaction in beta estimates (double subtraction) from each ROI, correlated with WM probe and visual search RT task performance measures (n = 28).
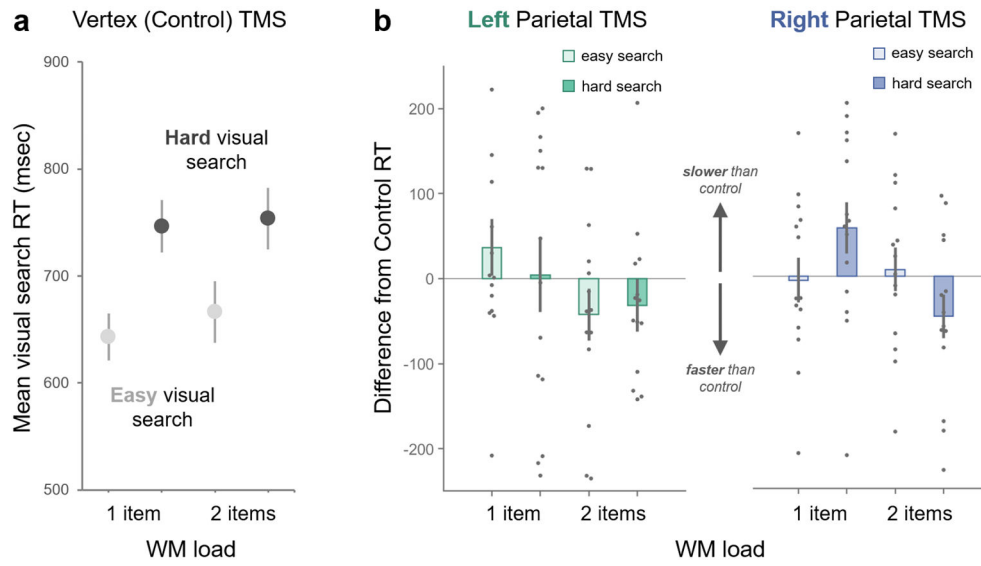
Figure 3.
a) Visual search RT during control TMS condition (vertex stimulation), replicating Kiyonaga et al., 2017. b) The impact of experimental TMS on visual search RT for contralateral targets. Plots display difference scores, relative to vertex TMS, to illustrate the effect of left and right parietal TMS at each level of WM load and visual search difficulty. Plots depict only search for targets in the visual hemi-field contralateral to TMS. Individual points represent mean difference scores for each individual subject. For both (a) and (b), error bars represent SEM and lighter shades denote easy search conditions whereas bold shades denote hard search conditions.

Table 1.

WM probe accuracy for all conditions

		Easy Search				Hard Search			
		1 item		2 items		1 item		2 items	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
	Vertex	**92.5%**	7.5%	**80.7%**	9.8%	**91.1%**	8.5%	**79.3%**	11.5%
TMS Site	**Left Parietal**	**89.3%**	12.8%	**77.9%**	12.1%	**90.0%**	8.9%	**78.6%**	7.5%
	Right Parietal	**82.9%**	18.6%	**72.9%**	18.8%	**80.4%**	18.8%	**75.0%**	18.3%