Goal-dependent dissociation of visual and prefrontal cortices during working memory

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To determine the specific contribution of brain regions to working memory, human participants performed two distinct tasks on the same visually presented objects. During the maintenance of visual properties, object identity could be decoded from extrastriate, but not prefrontal, cortex, whereas the opposite held for nonvisual properties. Thus, the ability to maintain information during working memory is a general and flexible cortical property, with the role of individual regions being goal-dependent.

The role of individual regions (including parietal, extrastriate and prefrontal cortex) during working memory has long been debated (for example, ref. 1). Early proposals suggested that lateral prefrontal cortex (lPFC) both controls working memory and directly maintains information. In contrast, more recent studies specifically of visual working memory have suggested that, whereas lPFC initiates and controls working memory, maintenance occurs in posterior cortices[2,3]. This new evidence has relied on multivariate analyses showing that the contents of visual working memory can be decoded from occipitotemporal[2,4–6] and parietal[3] (but see refs. 2,6) cortex but not the lPFC[2,3], despite activation in all regions. However, there is also evidence that lPFC plays a role in the maintenance of nonvisual (for example, verbal or conceptual) content. For example, impairments have been reported with transcranial magnetic stimulation to the lPFC during the maintenance of nonvisual but not visual information[7].
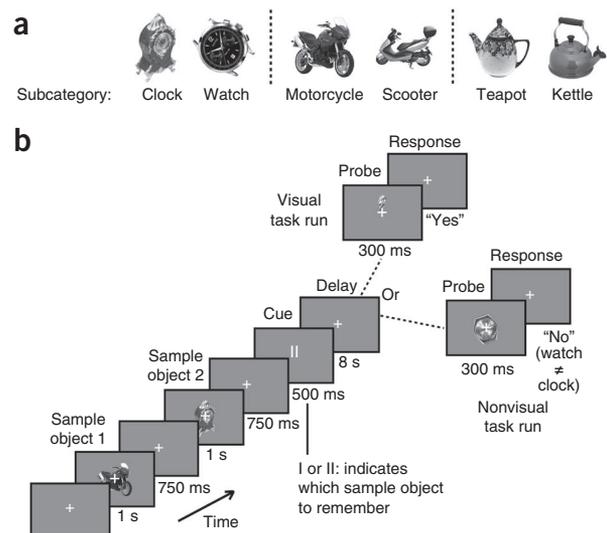
To reconcile these findings, we propose that the functional role of regions within the working memory network is flexible, dependent on the nature of maintained information. To test this hypothesis, we designed an experiment in which the same visual stimuli were presented but the maintained information differed due to task demands.

Participants saw two sample objects (**Fig. 1a**) before being cued as to which object was relevant for that trial (see also ref. 4). In visual task runs, participants had to indicate whether the probe (an object fragment) belonged to the cued object or not, requiring the maintenance of visual features. In nonvisual task runs (**Fig. 1b**), participants had to indicate whether the probe (a whole object) was from the same subcategory as the cued object or not, requiring the maintenance of the name or subcategory of the object. This equated the stimulus presentation across tasks. We also used ultra-high-field (7 T) functional magnetic resonance imaging (fMRI) to collect high-resolution data (1.8-mm isotropic voxels) across the whole brain to test decoding across the entire working memory network simultaneously (see ref. 8 for a discussion of the importance of decoding in these investigations).

To verify the nature of the information maintained during the delay period of each task, we first performed a separate behavioral study outside the scanner (**Fig. 2a**). During the delay, we presented either visual object or word distractors and measured their impact on task performance. To ensure that participants actively processed the distractors, they had to respond whenever they saw a nonsense object or word in the sequence. The visual object distractors impaired performance on the visual more than the nonvisual task, whereas the word distractors showed the opposite pattern, yielding a highly significant interaction in a two-way ANOVA between task (visual, nonvisual) and distractor type (object, word) ($F_{1,13} = 15.05$, $P < 0.01$). These results establish the maintenance of visual information during the visual task and nonvisual information during the nonvisual task (**Fig. 2b**).

In the fMRI experiment, a separate group of participants performed either the visual or nonvisual task (with no distractors) in each of

Figure 1 Experimental design. (**a**) Object images were from three broad categories (separated by dotted lines) with two subcategory exemplars each. (**b**) Visual and nonvisual tasks were performed in separate runs and required maintenance of either visual or nonvisual information during the delay period. In both tasks, two objects were presented sequentially, followed by a cue, a delay and a probe image. In the visual task, the probe was a partial object image, and participants indicated whether it came from the cued object. In the nonvisual task, the probe was a whole object image, and participants determined whether it was from the same subcategory as the cued object.

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Figure 2 Nature of maintained information. (**a**) Distractors presented during the delay period of the visual or nonvisual task. Participants responded whenever they saw a nonsense object or nonword (green outlines). (**b**) The visual task was more impaired with object than word distractors, whereas the opposite was true in the nonvisual task. Bars show the mean reaction time difference between the two distractor types in the two tasks across participants ($n = 14$). Error bars indicate between-subjects s.e.m. $*P < 0.05$, $t_{13} > 1.98$.
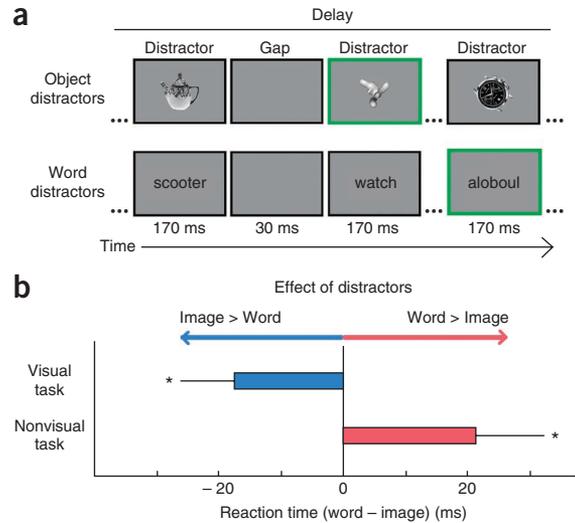
eight interleaved runs (**Fig. 1b**, **Supplementary Table 1**). The primary analyses focused on two regions of interest (ROIs), lateral prefrontal cortex (lPFC) and posterior fusiform cortex (pFs), identified in independent localizer scans (**Fig. 3a**; see **Supplementary Figs. 1** and **2** for whole-brain analyses). lPFC is commonly activated in working memory studies[9,10], and pFs is thought to be involved in the high-level processing and memory for visual objects[11].

During the delay period of each task, both lPFC and pFs were active, but there was no difference in the BOLD response magnitude in either ROI (**Fig. 3b** and **Supplementary Figs. 1** and **3**). A two-way ANOVA with task and ROI (lPFC, pFs) as within-subject factors revealed only a main effect of ROI ($F_{1,21} = 23.75$, $P < 0.01$) and no main effects or interactions involving task (all $F_{1,21} < 2.72$, $P > 0.11$).

We next trained support vector machines (SVMs) on the patterns of response during the delay period to test whether the identity of the maintained object could be decoded[8]. We observed stronger decoding during the maintenance of visual than nonvisual properties in pFs, whereas the opposite was true in lPFC (**Fig. 3c** and **Supplementary Figs. 2** and **4**). A two-way ANOVA with ROI and task as within-subject factors revealed a highly significant interaction between ROI and task ($F_{1,21} = 11.44$, $P < 0.01$) but no main effects (both $F_{1,21} < 0.04$, $P > 0.84$). In pFs, decoding during the visual ($t_{21} = 2.67$, $P < 0.01$) but not nonvisual ($t_{21} = -0.12$, $P > 0.45$) task was significantly greater

a pFs   lPFC
Ant — Pos   Ant — Pos
Object-selective localizer   Category-task localizer

than chance and there was a significant difference between them ($t_{21} = 2.07$, $P < 0.05$) (**Fig. 3c**). In lPFC, we observed the opposite pattern (**Fig. 3c**), with significant decoding during the nonvisual ($t_{21} = 1.73$, $P < 0.05$) but not visual task ($t_{21} = -0.37$, $P > 0.35$) and a significant difference between them ($t_{21} = 2.31$, $P < 0.05$). These results demonstrate a task-dependent functional dissociation between prefrontal and posterior cortices, with decoding during the delay determined by the nature of the maintained information. Thus, both prefrontal and posterior cortices are capable of maintaining information during working memory but are directly involved only in the maintenance of the types of information they generally process: visual object identity information in pFs (see, for example, ref. 12) and verbal or conceptual information in lPFC[7].

This framework may help reconcile the results of previous studies of lateral prefrontal cortex. Our results for the visual task are consistent with recent visual working memory studies emphasizing the role of prefrontal cortex only in the control of working memory[3,6]. Further, our results for the nonvisual task are consistent with transcranial magnetic stimulation data[7] and with single-cell recording results in monkeys[13] that strongly suggest information maintenance in lateral prefrontal areas for abstract information. Notably, prefrontal cortex appears capable of both control (for example, ref. 14) and maintenance in certain contexts, necessitating a reformulation of its general role in working memory. Future studies will need to shed light on whether these two functions arise from the same neuronal populations or from nearby but distinct populations.

Although we did not find any significant difference between tasks in the posterior parietal cortex (**Supplementary Fig. 5**), our formulation of working memory might also resolve a debate[15] about whether the parietal cortex is directly involved in maintenance[3] or only in control[2]. Parietal involvement in maintenance has been found for complex visuospatial patterns[3], which it is generally involved in
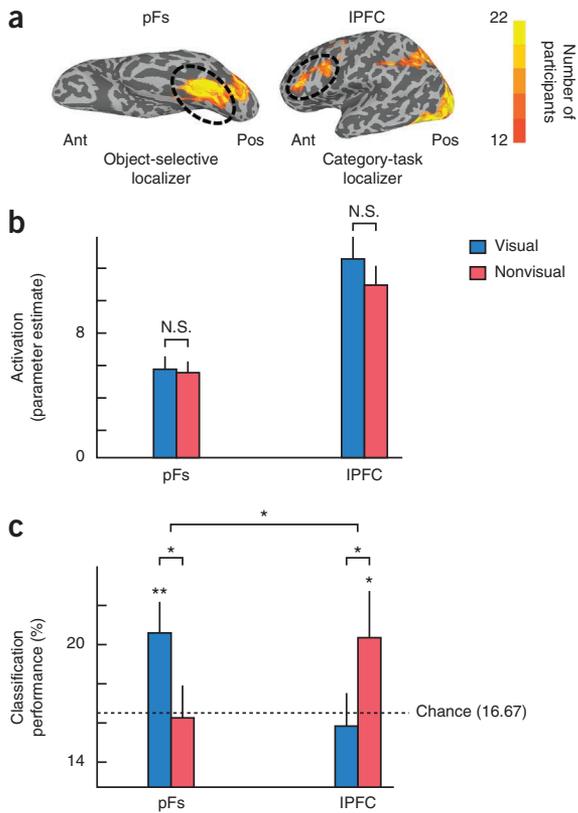
Figure 3 Decoding of object identity. (**a**) Overlap map across participants ($n = 22$) for object-selective and category-task localizers (see Online Methods) showing location of pFs and lPFC ROIs (dashed outlines) on inflated ventral (left panel) and lateral (right panel) surfaces. Ant, Anterior; Pos, posterior. (**b**) Parameter estimate (arbitrary units). There was no effect of task on response magnitude. N.S., not significant. (**c**) Decoding of object identity was significantly greater for the visual than nonvisual task in pFs, whereas the opposite was true in lPFC. $*P < 0.05$; $**P < 0.01$. Error bars indicate between-subjects s.e.m.

processing (see ref. 16 for a review), but not for simple direction or speed, which are maintained in more posterior areas[2].

Our results add to growing evidence for the importance of internally generated top-down signals in defining representations in visual areas (for example, imagery[17] or color knowledge[18]). Further research is needed to better understand both how these top-down signals interact with stimulus-driven processing and whether and how phenomenologically distinct processes, such as working memory, imagery and attention, differ from one another in these cortical areas.

In summary, our results suggest that working memory depends on behavioral goals, with this context determining both the nature of the maintained information and the cortical regions involved. These results imply that the ability to maintain information is a general property of cortex, flexibly engaged in accordance with behavioral goals. This model of working memory suggests a highly adaptable mechanism and has implications for the function of many regions throughout the cortex.

METHODS

Methods and any associated references are available in the online version of the paper.

Note: Supplementary information is available in the online version of the paper.

AUTHOR CONTRIBUTIONS

S.-H.L., D.J.K. and C.I.B. designed the research. S.-H.L. performed the research and analyzed the data. D.J.K. contributed analytic tools. C.I.B. supervised the project. S.-H.L., D.J.K. and C.I.B. wrote the manuscript.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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ONLINE METHODS

Participants. Twenty-two neurologically intact and right-handed participants (age 25.50 ± 1.21 years, 11 female) took part in the fMRI experiment. Two additional participants were excluded because they did not respond in either task for more than 40% of trials. No statistical test was run to predetermine sample sizes. The sample size was justified on the basis of other working memory studies using MVPA[3]. Fourteen additional neurologically intact and right-handed participants (age 24.57 ± 1.16 years, 7 female) took part in the behavioral experiment with distractors. All participants provided written informed consent for the procedure in accordance with protocols approved by the NIH Institutional Review Board.

Tasks and stimuli. Two specific memory tasks (visual, nonvisual) were performed in both the fMRI and behavioral experiments in separate runs. Each task required the maintenance of either visual or nonvisual properties of the same set of sample objects. There were six sample object images: clock, watch, motorcycle, scooter, teapot and kettle, consisting of three pairs of objects from the same general category but with distinct subcategory names (for example, clock and watch) (**Fig. 1a**).

Each run contained one task, and before each run participants were instructed what task they would perform (**Fig. 1b**). On each trial of both tasks, a participant saw two unrelated sample objects presented sequentially, followed by a cue indicating which object had to be remembered during delay period (see also ref. 4) (**Fig. 1b**). After the delay period, a probe image was presented. Participants indicated their match/nonmatch judgment via a button box, and the button that indicated each response type was counterbalanced across participants.

In the visual task, the probe was an object fragment either from the cued image or from the other image in its general category. Participants were instructed to press the 'yes' button if the fragment image belonged to the cued object and otherwise press the 'no' button as quickly as possible. The size of the object fragment was approximately 1/12 of the whole object. This fragment size was chosen to force participants to maintain detailed visual information.

In the nonvisual task, the probe was a whole object image either from the same or different but matched subcategory as the cued object (for example, watch and clock). Participants were instructed to press 'yes' for the probe that was the same subcategory as the cued object and otherwise press 'no' as quickly as possible. Every trial of this nonvisual task contained a new probe image, which was never presented as a sample image and never reused on other trials. This probe required the participants to maintain the subcategory name of the cued object and rendered visual information ineffective in making the matching judgment. No specific strategy for performing each task was provided to the participants.

fMRI experiment. Each task was presented in four scan runs consisting of 24 trials each. In each trial, two sample object images were presented sequentially with 1-s duration for each and 750-ms intersample interval. A roman numeral cue (I or II) was then presented for 500 ms, followed by an 8-s delay and a 300-ms probe. This cue indicated whether the first or second sample object was to be remembered across the delay. The length of each trial was 14 s and the inter-trial interval (ITI) varied, with an average ITI of 6 s. The order of the sample objects and cues was randomized and counterbalanced across runs. Two scan runs of each task (thus 48 trials) included the full set of the presentation cases for all of the possible first and second objects and cues.

Behavioral experiment with distractors. The behavioral experiments closely mirrored the fMRI experiments (**Fig. 2a**), with the following exceptions. During the delay period, whose length varied (3.0, 3.8 or 4.8 s), a sequence of either visual object or word distractors was presented. Object distractors were one of the four sample objects not used in that trial. Word distractors were the subcategory names of those same four images. These two types of distractors were presented during each of the two types of task, leading to a 2×2 factorial design: distractor type (object, word) $\times$ task (visual, nonvisual). This experimental design allowed us to test what information was being maintained in each task, by testing for a selective effect of each type of distractor in each task.

To further increase the salience and effectiveness of the distractors, targets requiring a response were embedded in the sequence (object: abstract embryos[19]; words: nonwords (http://www.neuro.mcw.edu/mcword/)) (**Fig. 2a**;

green squares). During each sequence, either one or two target embryos or nonwords were presented, and participants pressed a button whenever they saw a target. In both word or object distractor sequences, each distractor was presented for 170 ms, with a 30-ms interval preceding the next distractor, during which only a fixation cross was presented. The first distractor was presented 500 ms after the initiation of the delay period, and the last distractor was presented 900 ms before the termination of the delay period. When the length of the delay period was 3.0, 3.8 or 4.8 s, each potential distractor was repeated two, three or four times, respectively. The number of targets embedded in the distracter sequence also scaled with the duration of the delay period (3.0 and 3.8 s: one target; 4.8 s: two targets).

For the analyses of reaction time, median values were used to limit the influence of outliers. As in the fMRI experiment, each task was presented in separate runs, with four runs of 48 trials each for each task with distractor type balanced across trials in each run. The order of the distractor sequences, distractor types (object, word), cues and objects were randomized and counterbalanced.

Localizer design. The regions of interest (ROIs) used for analysis were determined by two localizer scans (**Fig. 3a**). The object-selective localizer was used to identify object-selective regions of cortex. Participants viewed alternating 16-s blocks of grayscale object images and retinotopically matched scrambled images[17]. The resulting object-selective lateral occipital complex (LOC) can be divided into an anterior ventral (pFs) (**Fig. 3a**; left) and a posterior dorsal part (LO) (**Supplementary Fig. 5d**). The category task localizer was used to identify areas involved in processing the object category and/or name information required during the nonvisual task. During this localizer scan, participants performed alternating 24-s blocks of an object category and a color detection task. In the object category blocks, participants were presented object images and pressed the button whenever they saw two of the same object category in a row. In color detection blocks, participants were presented with just a fixation cross, periodically changing in color, and pressed the button whenever they saw a red fixation cross. During each 24 s block, participants had to respond three times. The resulting regions were found in the frontal, parietal and visual cortices (**Fig. 3a**, right). Lateral prefrontal regions were used as lPFC in the later analyses (**Fig. 3b,c** and **Supplementary Figs. 3** and **4**), as was the activated region in the posterior parietal cortex (**Supplementary Fig. 5a–c**). Because there was no significant difference in the results between the left and right hemispheres in each ROI, analyses were collapsed across hemispheres.

fMRI data acquisition. Participants were scanned on the 7-T Siemens scanner at the fMRI facility on the NIH campus in Bethesda. Images were acquired using a 32-channel head coil with an in-plane resolution of 1.78×1.78 mm and 52 1.8-mm slices (0.18-mm inter-slice gap, repetition time (TR) = 2 s, echo time (TE) = 25 ms, matrix size = 108×108, field of view (FOV) = 192 mm). Whole brain volumes were scanned, and our slices were oriented approximately parallel to the base of the temporal lobe. All functional localizer and main task runs were interleaved. Standard MPRAGE (magnetization-prepared rapid-acquisition gradient echo) and corresponding GE-PD (gradient echo–proton density) images were collected before the experimental runs in each participant, and the MPRAGE images were then normalized by the GE-PD images for use as a high-resolution anatomical data for the following fMRI data analysis[20].

fMRI data analysis. Data analysis was conducted using AFNI (http://afni.nimh.nih.gov/afni/)[21], SUMA (AFNI surface mapper), FreeSurfer and custom MATLAB scripts. Data preprocessing included slice-time correction, motion correction and smoothing. Smoothing was performed only for the localizer data, not the event-related data, with Gaussian blur of 5 mm full-width half-maximum (FWHM).

To derive the BOLD response magnitudes during the visual and nonvisual tasks, we deconvolved the responses using the AFNI software package (3dDeconvolve using TENT function with motion parameters and up to fourth-order polynomials treated as regressors of no interest) and derived the β-value of each voxel for each of the ten TRs 0–18 s after the initiation of each trial. The response magnitudes during the delay period were produced by averaging the β values of individual voxels across the TRs 6–10 s after the onset of each trial (**Fig. 3b** and **Supplementary Figs. 1** and **5b,e**). To visualize ROI-specific response, the response magnitudes were averaged across all voxels within each ROI at each

TR (**Supplementary Fig. 3**) or averaged across the delay period (**Fig. 3b** and **Supplementary Fig. 5b,e**).

To decode maintained information, we used multiclass classification using a linear support vector machine (SVM) approach. We used the LIBSVM package developed by Chang and Lin (http://www.csie.ntu.edu.tw/~cjlin/libsvm/). The four runs of each task were divided into two halves, each of which included the full set of the presentation cases (see "fMRI experiment" section above), in two possible ways. For each of the splits, β values were extracted from the voxels within each ROI (the ROI analyses) or a sphere (radius 6.3 mm, corresponding to ~123 voxels) across the whole brain (the searchlight analysis[22]) and then normalized in each voxel by subtracting the mean value across all object conditions[17,23]. To decode the information during the delay period of each task, the patterns of the response averaged across time points 6–10 s (after the onset of each trial) from half of the total four runs of each task were used to train a classifier for cued object identity, and the patterns averaged across time points 6–10 s from the other half were used to determine the classification accuracy, exhaustively (**Fig. 3c** and **Supplementary Figs. 2** and **5c,f**). For the decoding analysis at each TR, the linear classifier was trained using the response from TRs corresponding with 6–10 s following trial onset, but then tested on all ten TRs (**Supplementary Fig. 4**)[4]. All the main analyses of the fMRI data included data from all trials, as an incorrect response does not necessarily indicate that the wrong object was held in memory. Identical analyses performed on only the correct trials revealed nearly identical results. A two-way ANOVA with ROI and task as within-subject factors on decoding results based only on the correct trials revealed a highly significant interaction between ROI and task ($F_{1,21}$ = 13.52, $P < 0.01$) but no main effects of ROI or task (both $F_{1,21} < 0.02$, $P > 0.89$).

We also performed the same decoding analyses on the basis of the response of an anatomically defined lateral prefrontal cortex. For this analysis, we used a rostral-middle-frontal region defined by the cortical parcellation of FreeSurfer[24]

and found nearly identical results to those from functionally defined lPFC. While the BOLD response magnitudes did not show any significant difference between tasks (t_{21} = 0.74, $P > 0.46$), decoding during the nonvisual task (but not visual task) was significantly greater than chance (t_{21} = 3.11, $P < 0.01$) and greater than that during the visual task (t_{21} = 3.18, $P < 0.01$).

Before mapping data from the activation or searchlights to the standard-mesh surfaces reconstructed by AFNI and SUMA (**Supplementary Figs. 1** and **2**)[25], we smoothed the analyzed data with a Gaussian blur of 5 mm FWHM.

Statistical analyses. As all comparisons were planned, to compare activation or decoding results with basal level (zero or chance level, respectively), we used one-sample *t*-tests (one-tailed). When we compared behavior, activation or decoding results between tasks, we mainly used two-way ANOVAs (tests of within-subjects effects) to examine the effects of ROI (or distractor), task and the interaction between them. If any interaction effect was revealed, we used one-tailed paired *t*-tests to examine detailed effects between tasks with the assumption of predicted direction. Otherwise, we used two-tailed paired *t*-tests. To reveal the effects of ROI, task, time points and their interactions, we used three-way ANOVAs (tests of within-subjects effects). Greenhouse-Geisser corrections were used for all ANOVAs with factors with more than two levels. Error bars in all plots indicate 1 between-subjects s.e.m.

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