Neural correlates of spatial working memory manipulation in a sequential Vernier discrimination task

Juan M. Gutiérrez-Garralda[a], Carlos R. Hernandez-Castillo[a], Fernando A. Barrios[b], Erick H. Pasaye[b] and Juan Fernandez-Ruiz[a]

Visuospatial working memory refers to the short-term storage and manipulation of visuospatial information. To study the neural bases of these processes, 17 participants took part in a modified sequential Vernier task while they were being scanned using an event-related functional MRI protocol. During each trial, participants retained the spatial position of a line during a delay period to later evaluate if it was presented aligned to a second line. This design allowed testing the manipulation of the spatial information from memory. During encoding, there was a larger parietal and cingulate activation under the experimental condition, whereas the opposite was true for the occipital cortex. Throughout the delay period of the experimental condition there was significant bilateral activation in the caudal superior frontal sulcus/middle frontal gyrus, as well as the insular and superior parietal lobes, which confirms the findings from previous studies. During manipulation of spatial memory, the analysis showed higher activation in the lingual gyrus. This increase of activity in visual areas during the manipulation phase fits with the hypothesis that information stored in sensory cortices becomes reactivated once the information is needed to be utilized. *NeuroReport* 00:000–000 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.

NeuroReport 2014, **00**:000–000

Keywords: alignment, functional MRI, linear projection, spatial working memory, Vernier, visual cortex

[a]Department of Physiology, Faculty of Medicine, National Autonomous University of Mexico and [b]Institute of Neurobiology, National Autonomous University of Mexico

Correspondence to Juan Fernández-Ruiz, PhD, Department of Physiology, Faculty of Medicine. National Autonomous University of Mexico, Mexico City, Mexico. 04510, Mexico
Tel: +52 55 56232393; fax: +52 55 56232241; e-mail: jfr@unam.mx

Received 3 September 2014 **accepted** 17 September 2014

Introduction

According to Baddeley's theory, the term working memory refers to a brain system that is involved in temporary storage and manipulation of information. Initial functional imaging studies on the neural basis of spatial working memory (SWM) have focused mainly on the storage component and have laid out a general neural circuitry that includes specific prefrontal and parietal cortices [1–4]. Typically, these SWM tasks use an array of one or more items whose location needs to be maintained in mind during a delay period with no stimuli present. However, few studies have addressed the discrimination and manipulation of SWM content during alignment tasks [5,6].

To delve into the neural bases of the spatial manipulation component during a working memory task, we used a sequential Vernier task that allows making a different manipulation of the spatial component. In this paradigm, participants were instructed to judge whether two lines were aligned when there was a delay period between them [5]. A characteristic of this task is that, to decide, participants have to compare the probe's spatial location not with the spatial location of the initial array stored in mind, but with a projection of that spatial location – that is, to compare both stimuli, participants have to manipulate the spatial location stored in their memory and decide whether it is aligned to the current probe. This setup would provide a more clear evaluation of the neural bases of the spatial information manipulation in contrast to spatial tasks that require responding whether a new item is shown in the remembered location of the standard stimulus.

Materials and methods

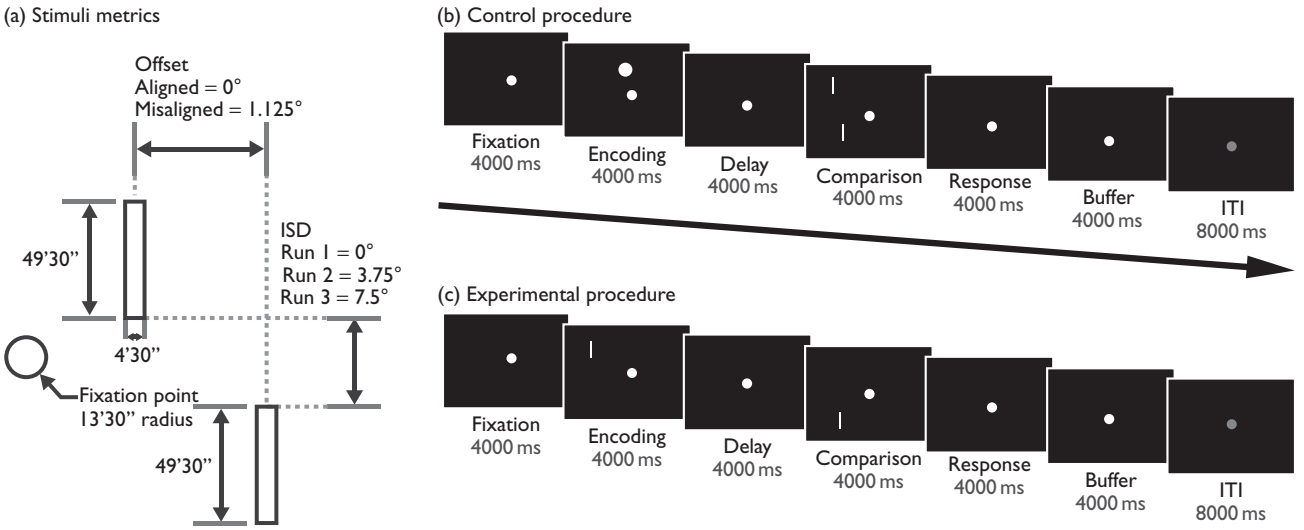
Task and procedure

The task was designed after a modified hyperacuity test developed by Matin *et al.* [5]. Participants are asked to decide whether two lines are aligned (Fig. 1). In our case, all misaligned stimuli were offset by 1.125°, whereas aligned trials remained at 0°. The variable used to provide a parametrical change of the spatial domain was the interstimulus distance (ISD), which was the space separating the two lines; three different ISDs were tested: 0°, 3.75°, and 7.5° (Fig. 1a). The lines were presented vertically or horizontally in a semirandomized manner.

We tested two conditions. Under the experimental condition, participants encoded the location of the line (standard stimulus) during the encoding phase to maintain it during the delay phase (Fig. 1c). Thereafter, participants were presented with the comparison stimulus, which was presented aligned or misaligned to the previously memorized stimulus, and participants had to judge accordingly. The control procedure was similar,

0959-4965 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/WNR.0000000000000280

Fig. 1



(a) Stimuli metrics. Schematic illustration of the time course for the (b) control and (c) experimental procedures. ISD, interstimulus distance; ITI, Inter-trial interval.

except participants did not encode spatial information. Instead, they were presented with a white disc, which signaled the beginning of a control trial (Fig. 1b). This disc contained equivalent visual stimulation to the experimental counterpart. Thereafter, both stimuli were presented at the same time during the comparison phase. Participants responded with key presses, signaling whether the stimuli had appeared aligned or misaligned during the response period only. Participants responded by pressing one of two buttons affixed to their hands using ResponseGrips (NordicNeuroLab, Bergen, Norway). Responses were pseudorandomized by assigning half of the sample to respond by pressing the thumb button on the grips when the stimuli had been presented aligned to each other and pressing the index finger button when the stimuli were misaligned. Participants maintained the same response assignment throughout the trial. This variation was applied to avoid response biases due to the finger being used to respond. There were no significant behavioral or accuracy differences between the assigned groups. Under the experimental and control conditions, participants were instructed to respond after stimuli were no longer visible. Each participant took part in three runs, each of which tested a different interstimulus distance. Experimental and control trials were presented semirandomly within each run. Likewise, the order in which the runs were presented to the participants was also randomly determined. Two behavioral responses (of 288) were not received during the allotted 4-s response block and were excluded from the analysis.

Participants and image acquisition

Seventeen right-handed participants (12 male, five female), ages 19–47 years ($M = 32.9$, $SD = 9.41$) were scanned on a 3.0 T Discovery MR750 General Electric (GE Medical Systems, Waukesha, Wisconsin, USA) scanner with a 32-channel head coil. T_2*-weighted slices depicting BOLD signal were obtained during functional scans (35 slices with zero gap, TR = 2000 ms, TE = 40 ms, 64×64 matrix, field of view 256×256 mm, in isometric voxels of $4 \times 4 \times 4$ mm^3). For each participant, high-resolution T1-weighted anatomic images were also collected with an FSPGR sequence (256×256 matrix, field of view 256×256 mm, in isometric voxels of $1 \times 1 \times 1$ mm^3). For the stimuli presentation, we used a NordicNeuroLab system display at an SVGA, 800×600 pixel aspect ratio, 85 Hz, field of view 30° horizontal, 23° vertical. Tethered to the same visual system was an eye-tracking system using ViewPoint software (field of view 20 mm diameter; Arrington Research, Scottsdale, Arizona, USA) that recorded eye movement information to ensure proper fixation and engagement with the paradigm. All procedures were performed in accordance with the standards of the research ethics committees for human research of the Faculty of Medicine of the National Autonomous University of Mexico. All participants provided written informed consent for the application of the tests, in accordance with the Declaration of Helsinki.

Data preprocessing

Functional MRI (fMRI) data processing was carried out using the fMRI Expert Analysis Tool, Version 6.00, part

of fMRIB's Software Library (FSL; *http://www.fmrib.ox.ac.uk/fsl*). The following prestatistics processing was performed: motion correction using MCFLIRT [7], slice-timing correction using Fourier-space time-series phase-shifting, nonbrain removal using BET [8], spatial smoothing using a Gaussian kernel of full width at half maximum 5 mm, grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor, high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 50.0 s). Registration to high-resolution structural and MNI standard space images was carried out using FLIRT (FMRIB's Linear Registration Tool) [7] (2.4 fMRI Data Analysis).

fMRI data analysis

Time-series statistical general linear model analysis was carried out using FSL-FILM (FMRIB's Improved Linear Model) with local autocorrelation correction including the motion parameters as confounding variables [9]. Z (Gaussianized T) statistic images were thresholded using clusters determined by Z greater than 2.3 and a (corrected) cluster significance threshold of $P = 0.05$ [10]. The Generalized Linear Model included regressors aligned to the onset of each trial phase (encoding of standard stimulus, delay, comparison, and response) on the basis of the nature of the trial (control or experimental) and the ISD. In total, the Z-transformed Generalized Linear Model design matrix included 24 regressors.

Significant regions of interest (ROIs) were obtained after contrasts between each control and experimental Z-map. Significance was estimated by performing Monte Carlo simulations using the AFNI (Analysis of Functional NeuroImages, NIMH, Bethesda, Maryland, USA) 3dClustSim program (parameters were individual voxel $P > 0.01$, 20 000 simulations full width at half maximum 6 mm, with a mask of the whole brain), providing a corrected significance level of P less than 0.05. Clusters that did not meet this threshold were filtered out of the analysis. The resulting ROIs in the statistical whole-brain T-maps were anatomically assessed with the aid of the Talairach Atlas included in FSLview.

Results

Behavioral results

Participants made a few mistakes during the experiment. These mistakes did not differ significantly across variables. The effects of the two independent variables on the correct responses were analyzed using a Greenhouse–Geisser corrected, two-factor repeated-measures analysis of variance. The factors were the alignment between the stimuli and the ISDs. There were no significant main effects for either the alignment between the stimuli ($F_{1,17} = 0.028$, $P = 0.869$) or the ISD ($F_{1.472,25.031} = 0.157$, $P = 0.789$), with no significant interaction between the factors ($F_{1.82,30.93} = 0.127$, $P = 0.863$).

Neuroimaging results

Encoding of spatial information

Activity during the encoding phase was obtained by contrasting the predictors experimental encoding > control encoding. Significant activation was observed in the bilateral superior parietal lobe (BA 7), whereas a significant decrease was observed in the occipital cortex (BA 18). The cluster coordinates with significant differences in activity between the experimental and the control conditions are presented in Table 1.

Maintenance of spatial information

During the delay period of the trial, we identified ROIs by contrasting the predictors experimental delay > control delay. We found significant bilateral activity across different cortical areas, mainly in the middle frontal gyrus (BA 6), inferior frontal gyrus/insular cortex (BA4/13), and superior parietal (BA 7) regions. We also observed significant activity in the right lingual gyrus (BA 18; Fig. 2).

Manipulation of spatial information

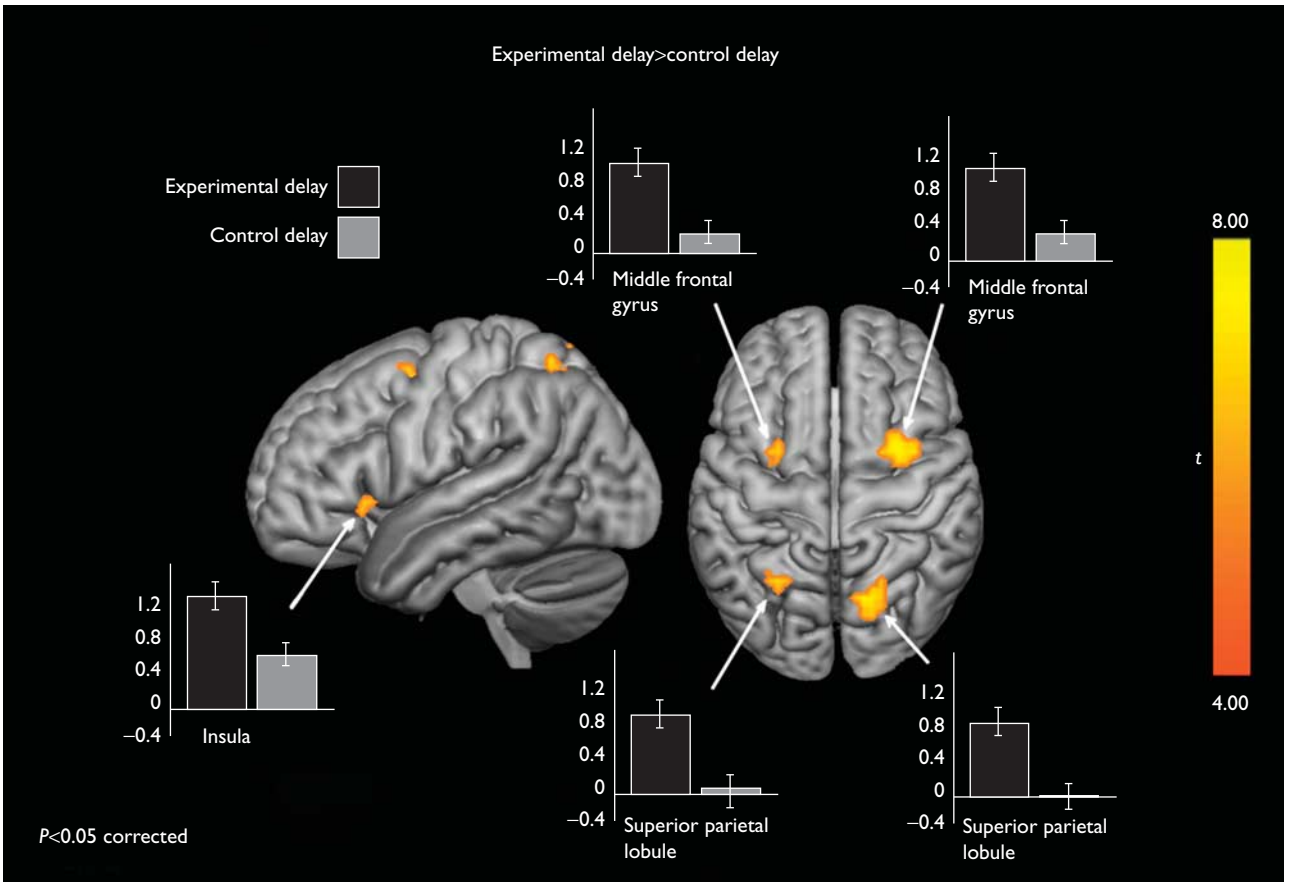
To find areas involved in the manipulation of spatial information, we applied a contrast with the predictors experimental comparison > control comparison. The results showed significant bilateral differences in the lingual gyrus (BA 18), and differences in the left thalamus and right dentate nucleus of the cerebellum due to increased activation during the experimental condition, that is, the manipulation of the stored spatial information (Fig. 3).

Table 1 Regions of interest

				ROI peak activation			
Contrast	Hem	Region of interest	BA	*x*	*y*	*z*	*t* (ROI)
Encoding experimental > encoding control							
	R	Superior parietal lobule	7	14	−66	60	7.46
	L	Cuneus	14	−68	16	−14	−6.8
Delay experimental > delay control							
	R	Superior parietal lobule	7	14	−66	60	6.04
	R	Middle frontal gyrus	6	30	2	52	6.38
	R	Insula	13	34	26	−4	6.05
	L	Middle frontal gyrus	6	−22	−2	52	5.29
	R	Lingual gyrus	18	22	−74	−8	5.65
	L	Superior parietal lobule	7	−26	−58	60	5.45
	L	Insula	13	−34	22	4	4.92
Comparison experimental > comparison control							
	L	Lingual gyrus	18	−6	−66	4	6.39
	L	Thalamus		−10	−18	0	5.55
	R	Culmen		14	−54	−20	4.9

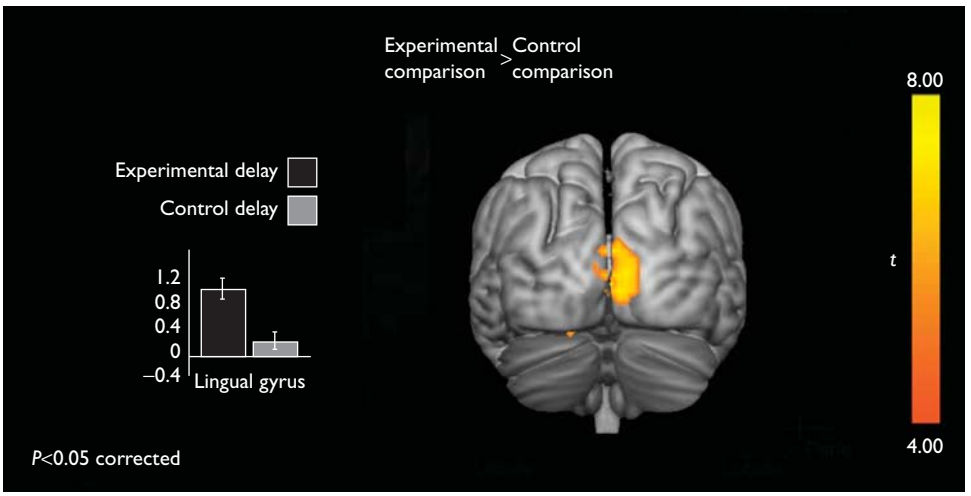
MNI coordinates for activation peak on each significant cluster. Anatomical information from the coordinates was obtained with Talairach Client included in FSL.
FSL, fMRIB's Software Library; ROI, regions of interest.

Fig. 2



Regions of interest with significant activity yielded through an experimental delay > control delay contrast. $P < 0.05$ corrected.

Fig. 3



Regions of interest with significantly larger activity during the decision period for the experimental compared with the control condition. Activity is present primarily at the lingual gyrus of the occipital lobe. $P < 0.05$ corrected.

Discussion

In this study we explored the neural basis of visuospatial working memory in a modified sequential Vernier task. With regard to the delay period, our results confirmed previous findings supporting a network involving prefrontal, insular, and parietal cortices [1–4]. However, the main advantage of using the modified Vernier task resided in the analysis of the manipulation of the temporarily stored information. The analysis of the manipulation phase shows significant differences depending on the information source, showing a larger activation, mainly in the occipital cortex, when the participants manipulated information stored in working memory.

Encoding and temporary retention of the standard stimulus position

The analysis of the encoding of spatial information for alignment discrimination shows significant bilateral activation in the superior parietal lobe (BA 7). This is in agreement with the notion that activity in this region is observed when spatial information is encoded [11]. As expected from any SWM task with high attentional demands, we also obtained significant activation in the parietal regions [12].

During the maintenance of the information, we found significant activation in the middle frontal gyrus (BA 6), inferior frontal gyrus/insular cortex (BA4/13), and superior parietal (BA 7) regions. These regions have previously been shown to be active during the delay in various working memory paradigms [13,14]. There was also significant activation in the right lingual gyrus (BA 18) [15]. This activity during the delay may be involved in the refreshing and maintenance of spatial information once it has been encoded or in the allocation of attention required to maintain the information in memory [16]. Activity in the insular region has also been reported previously in experiments designed to test imagining and scene-construction manipulation [17]. The lingual gyrus in the occipital lobe was also active across the delay, as it plays an important role in the basic steps of processing visual information [13,15] and memory maintenance [4,18,19].

Manipulation of the spatial information

To analyze the areas involved in the manipulation of the spatial information stored in working memory, we contrasted the experimental and control trials during the manipulation phase. This contrast revealed significant differences in a large area of the occipital cortex, which peaked in the lingual gyrus (BA18), and showed smaller activations in the thalamus and the dentate nucleus of the cerebellum, which have also been shown to be involved in working memory [20].

These results suggest that during an SWM task, early visual areas contribute to the spatial manipulation process. Previous findings have shown the contribution of early visual areas to visual memory related to priming [21], short-term memory [22], and working memory [15]. However, in the context of the sequential Vernier, the current findings suggest a more active participation that could be more related to mental imagery, involving a memory re-enactment of the position of the stimuli to verify its alignment [4,23–25].

Conclusion

Our analyses found activity in the early visual cortices during the manipulation of spatial information stored in working memory. This supports the hypothesis that during spatial working memory manipulation, there is an involvement of the primary sensory areas that initially coded the internalized stimulus [26]. We also propose that the Vernier delayed task could be used with other techniques, including phase encoding retinotopic mapping, to delve into the underlying SWM mechanisms.

Acknowledgements

This research was supported in part by a scholarship from CONACYT Convocatoria 290517 CVU 230047 to J.M. G.-G., who is a doctoral student from Programa de Doctorado en Ciencias Biomédicas, Universidad Nacional Autónoma de México. The authors also received support from grants from CONACYT 102312, PAPIIT-DGPA IN221413-3. They thank Juan José Ortiz and Leopoldo Gonzalez-Santos for their valuable contribution to this investigation.

Conflicts of interest

There are no conflicts of interest.

References

1 Courtney SM, Petit L, Maisog JM, Ungerleider LG, Haxby JV. An area specialized for spatial working memory in human frontal cortex. *Science* 1998; **279**:1347–1351.
2 Funahashi S, Bruce CJ, Goldman-Rakic PS. Dorsolateral prefrontal lesions and oculomotor delayed-response performance: evidence for mnemonic "scotomas". *J Neurosci* 1993; **13**:1479–1497.
3 D'Esposito M, Aguirre GK, Zarahn E, Ballard D, Shin RK, Lease J. Functional MRI studies of spatial and nonspatial working memory. *Brain Res Cogn Brain Res* 1998; **7**:1–13.
4 Jonides J, Smith EE, Koeppe RA, Awh E, Minoshima S, Mintun MA. Spatial working memory in humans as revealed by PET. *Nature* 1993; **363**:623–625.
5 Matin L, Pola J, Matin E, Picoult E. Vernier discrimination with sequentially-flashed lines: roles of eye movements, retinal offsets and short-term memory. *Vision Res* 1981; **21**:647–656.
6 Owen AM, Evans AC, Petrides M. Evidence for a two-stage model of spatial working memory processing within the lateral frontal cortex: a positron emission tomography study. *Cereb Cortex* 1996; **6**:31–38.
7 Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage* 2002; **17**:825–841.
8 Smith SM. Fast robust automated brain extraction. *Hum Brain Mapp* 2002; **17**:143–155.
9 Woolrich MW, Ripley BD, Brady M, Smith SM. Temporal autocorrelation in univariate linear modeling of FMRI data. *Neuroimage* 2001; **14**:1370–1386.
10 Worsley KJ. Statistical analysis of activation images. In: Jezzard P, Matthews PM, Smith SM, editors. *Functional MRI: an introduction to methods*. Oxford, New York: Oxford University Press; 2001. **xiii**:p. 390 pp.
11 Galletti C, Battaglini PP, Fattori P. Parietal neurons encoding spatial locations in craniotopic coordinates. *Exp Brain Res* 1993; **96**:221–229.

12 Yeh YY, Kuo BC, Liu HL. The neural correlates of attention orienting in visuospatial working memory for detecting feature and conjunction changes. *Brain Res* 2007; **1130**:146–157.
13 Courtney SM, Ungerleider LG, Keil K, Haxby JV. Transient and sustained activity in a distributed neural system for human working memory. *Nature* 1997; **386**:608–611.
14 Braver TS, Cohen JD, Nystrom LE, Jonides J, Smith EE, Noll DC. A parametric study of prefrontal cortex involvement in human working memory. *Neuroimage* 1997; **5**:49–62.
15 Cohen JD, Perlstein WM, Braver TS, Nystrom LE, Noll DC, Jonides J, Smith EE. Temporal dynamics of brain activation during a working memory task. *Nature* 1997; **386**:604–608.
16 Raabe M, Fischer V, Bernhardt D, Greenlee MW. Neural correlates of spatial working memory load in a delayed match-to-sample saccade task. *Neuroimage* 2013; **71**:84–91.
17 Hassabis D, Maguire EA. Deconstructing episodic memory with construction. *Trends Cogn Sci* 2007; **11**:299–306.
18 Awh E, Jonides J. Overlapping mechanisms of attention and spatial working memory. *Trends Cogn Sci* 2001; **5**:119–126.
19 Munneke J, Heslenfeld DJ, Theeuwes J. Spatial working memory effects in early visual cortex. *Brain Cogn* 2010; **72**:368–377.
20 LaBar KS, Gitelman DR, Parrish TB, Mesulam M. Neuroanatomic overlap of working memory and spatial attention networks: a functional MRI comparison within subjects. *Neuroimage* 1999; **10**:695–704.
21 Slotnick SD, Schacter DL. The nature of memory related activity in early visual areas. *Neuropsychologia* 2006; **44**:2874–2886.
22 Van de Ven V, Jacobs C, Sack AT. Topographic contribution of early visual cortex to short-term memory consolidation: a transcranial magnetic stimulation study. *J Neurosci* 2012; **32**:4–11.
23 Slotnick SD, Thompson WL, Kosslyn SM. Visual memory and visual mental imagery recruit common control and sensory regions of the brain. *Cogn Neurosci* 2012; **3**:14–20.
24 Le Bihan D, Turner R, Zeffiro TA, Cuénod CA, Jezzard P, Bonnerot V. Activation of human primary visual cortex during visual recall: a magnetic resonance imaging study. *Proc Natl Acad Sci USA* 1993; **90**:11802–11805.
25 Kosslyn SM, Behrmann M, Jeannerod M. The cognitive neuroscience of mental imagery. *Neuropsychologia* 1995; **33**:1335–1344.
26 Harrison SA, Tong F. Decoding reveals the contents of visual working memory in early visual areas. *Nature* 2009; **458**:632–635.