

# Increased prefrontal and parietal activity after training of working memory

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**Working memory capacity has traditionally been thought to be constant. Recent studies, however, suggest that working memory can be improved by training. In this study, we have investigated the changes in brain activity that are induced by working memory training. Two experiments were carried out in which healthy, adult human subjects practiced working memory tasks for 5 weeks. Brain activity was measured with functional magnetic resonance imaging (fMRI) before, during and after training. After training, brain activity that was related to working memory increased in the middle frontal gyrus and superior and inferior parietal cortices. The changes in cortical activity could be evidence of training-induced plasticity in the neural systems that underlie working memory.**

Working memory is the ability to retain information during short periods of time. The maximum amount of information that a person can retain in his or her working memory—the working memory capacity—is an important factor for determining problem solving and reasoning ability<sup>1–4</sup>. Regions in frontal and parietal cortices are important for working memory, and there is a positive correlation between brain activity in these regions and working memory capacity<sup>5–9</sup>.

It is largely unknown to what extent the neural systems that underlie working memory are plastic. One study has indicated that working memory systems are affected by training<sup>10</sup>. In that study, macaques practiced delayed-response tasks for several weeks, and the task difficulty was gradually increased by degrading the visual stimuli. Practice was found to change the receptive characteristics of neurons in the principal sulcus in the prefrontal cortex, such that they became more resistant to the effect of stimulus degradation. The effect of working memory training on cortical activity in healthy humans has, to our knowledge, not previously been investigated. The effect of repeated performance of a visuo-spatial working memory task has been studied, but the aim of that research was not to increase working memory capacity and the task was carried out during only one day<sup>11</sup>. Another study found that repeated performance with the same set of stimuli resulted in automation and decreased activity in task-related regions<sup>12</sup>. Increased activity after working memory training has been reported, but this was only shown in a single patient with schizophrenia<sup>13</sup>.

Adaptive and intensive training of working memory over a 5-week period leads to improved performance and a generalization of the training effect to nontrained tasks that are related to working memory and reasoning and are known to activate the prefrontal cortex<sup>14</sup> (T.K. *et al.*, unpublished data). In this study, we have focused on the neural correlates that are involved in the training of working memory and may underlie these changes in performance.

We report data from two imaging experiments of adult subjects undertaking training of working memory.

In Experiment 1, three subjects practiced three working memory tasks for 5 weeks. Brain activity was measured with fMRI twice before and once after training and was compared using a fixed-effect group analysis. During scanning, the subjects carried out a visuo-spatial working memory task and a control task. Increased activity after training was observed in prefrontal and parietal regions. To confirm the preliminary findings from Experiment 1, we carried out Experiment 2, which included eight subjects who were scanned five times each during the 5-week training period. We measured brain activity during the performance of a working memory task and a control task (Fig. 1) and used a random-effect analysis to measure any changes. The results confirmed the findings from Experiment 1 with training-induced increases in activity in prefrontal and parietal cortices.

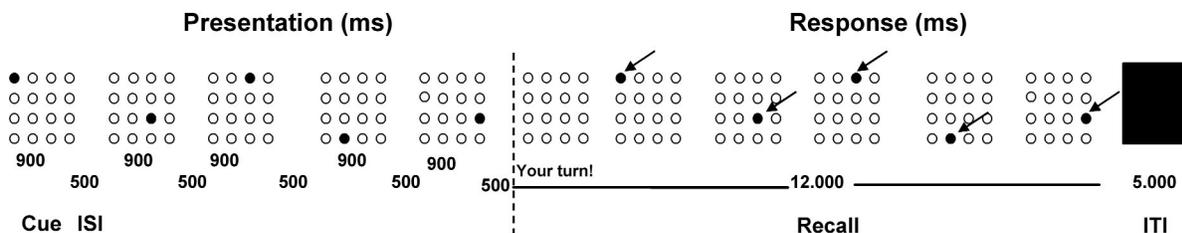
## RESULTS

### Experiment 1 - behavioral data

Three subjects practiced 90 trials per day for 20, 24 and 30 days, respectively, on three working memory tasks. The subjects were scanned before and after training. The working memory task that was done while the subject was in the scanner was designed to keep the error rate low. Thus, there were no significant differences in accuracy after training. There was, however, a tendency toward shorter reaction times ( $P = 0.14$ , paired  $t$ -test). Pre- and post-training scores on nontrained neuropsychological tests were used to determine whether the effect of working memory training generalized to non-trained tasks. Test-retest improvement was compared between the three subjects and a control group ( $n = 11$ ) that did not undertake training. Training significantly improved performance in the trained group ( $P < 0.05$ ) on the Span board task, Stroop time and Raven's Advanced Progressive Matrices.

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**Figure 1** Working memory task carried out during scanning in Experiment 2. Five or seven red circles (cues) were presented sequentially in a  $4 \times 4$  grid. Each cue was presented for 900 ms, with a 500-ms interstimulus interval (ISI). The cue presentation was followed by a blank grid and a text line indicating the start of the response phase, which lasted 12,000 ms. The subject indicated the location and order of the presented cues by clicking on a computer screen with an optic track-ball. The intertrial interval (ITI) was 5,000 ms after low-load trials and 2,200 ms after high-load and control trials. In the control task, seven green circles were presented sequentially in the two uppermost rows. The circles stayed on the grid when the text line appeared, and the task was to click them away in random order.

### Experiment 1 - fMRI scanning

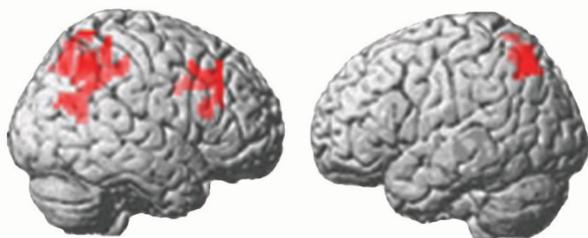
In a fixed-effect group analysis, training-induced increases in activity that was related to working memory were analyzed by looking at significant positive interactions between time (scans 1 and 2 versus scan 3) and task (control versus working memory task). Decreases were analyzed with negative time-by-task interaction. Positive interactions were found in the prefrontal and parietal cortices (Fig. 2). A negative interaction was found in the cingulate sulcus ( $x y z, -3 6 45$ ).

### Experiment 2 - behavioral data

Eight subjects practiced 90 trials per day for 5 weeks ( $18.0 \pm 3.1$  days; mean  $\pm$  s.d.) on three visuo-spatial working memory tasks. Performance during training gradually improved on all tasks (Fig. 3a). In contrast to Experiment 1, the working memory task carried out while the subject was in the scanner was more difficult and involved reproducing all of the memorized cues. Performance in the scanner improved over time on both load 5 and 7 (Fig. 3b;  $P < 0.05$ , paired  $t$ -test). Reaction time decreased over time (Fig. 3c;  $P < 0.05$ , paired  $t$ -test). For the nontrained neuropsychological tests, the subjects improved significantly on the Span board task ( $P = 0.05$ ), the Digit span task ( $P = 0.007$ ) and Stroop time ( $P < 0.01$ ). Compared with test-retest improvement in the control group ( $n = 11$ ), the training group improved significantly on Stroop time ( $P < 0.05$ ). The corresponding  $P$  values for the Span board task and Digit span task were 0.12 and 0.09, respectively.

### Experiment 2 - mnemonic strategies

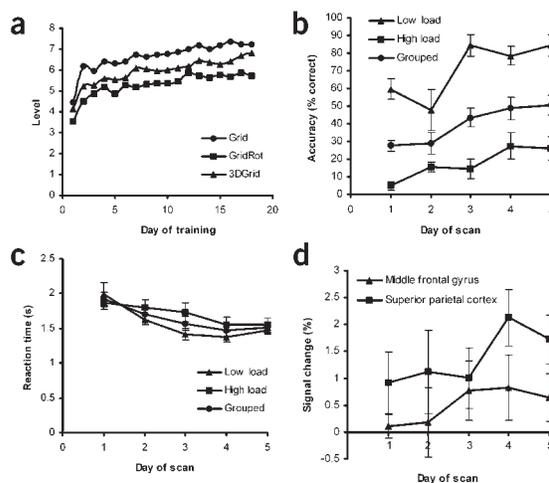
We used two approaches to quantify possible encoding strategies and to see whether the use of these strategies changed during training: written interviews after training and statistical analysis of training



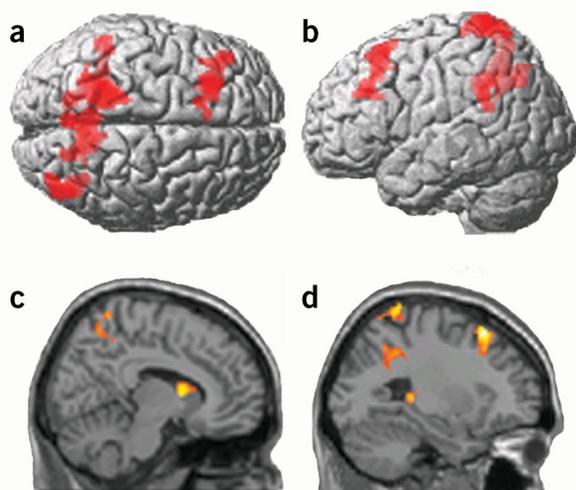
**Figure 2** Increase in brain activity after working memory training (Experiment 1). Subtraction images of mean responses from the fMRI analysis were overlaid on a single-subject T1-weighted image. Regions with an increase in brain activity after training were found in the right middle frontal gyrus ( $x y z, 36 21 18$ ;  $t = 3.9$ ), in the right inferior parietal cortex ( $42 -57 45$ ;  $t = 4.1$ ) and bilaterally in the intraparietal cortex ( $18 -69 48$ ,  $t = 6.6$ ;  $-15 -69 60$ ,  $t = 5.6$ ).

data. In the interviews, six subjects reported that they used chunking as a strategy and that this strategy was constant during the training period. Chunking refers to the association of different items into units that are remembered as a whole, thereby facilitating encoding. The two subjects who reported that they did not use chunking were also the only two who reported that they changed strategies, which occurred after about a week.

For the second approach, we analyzed 4,320 trials from the training data of all subjects. We evaluated six different stimuli factors to deter-



**Figure 3** The effect of working memory training on performance and signal change (Experiment 2). (a) Performance during training. The average increase in task performance is shown for eight subjects on Grid, Grid rotation and 3D Grid during 18 days of working memory training (standard errors were too small to be seen on this scale). Working memory training started the first day on level 2 (a sequence with two cues) for all tasks. Difficulty was adjusted to performance, and on each following day of training the starting level corresponded to the level that had been reached on the previous day. (b) Accuracy in percent correct trials (mean  $\pm$  s.e.m.) for working memory trials done during scanning. Accuracy was defined as the number of correctly recalled trials during one scan multiplied by the number of cues for low-load trials, high-load trials and low- and high-load trials grouped together. (c) Response time (mean  $\pm$  s.e.m.) for working memory trials (as in b) done during scanning. Response time was defined as the average time for one response click when recalling the presented sequence. (d) Change in activity that is related to working memory over time in the superior parietal cortex ( $x y z, -4 -70 46$ ) and middle frontal gyrus ( $-26 22 56$ ). The points represent mean signal change for all subjects during each scan. The percent signal change refers to signal change with respect to a whole-brain mean activity of 100.



**Figure 4** Regions where brain activity correlated with increased working memory capacity (Experiment 2; **Table 1**). (a) Top view. (b) Left hemisphere. The increased activity in the left middle frontal gyrus and bilaterally in the superior and intraparietal and inferior parietal cortex, rendered onto the surface of the brain. (c) Sagittal section showing the increase in the caudate nucleus ( $x\ y\ z$ , 10 8 12). (d) Sagittal section showing the increase in the middle frontal gyrus ( $-6\ 22\ 56$ ), superior and intraparietal and inferior parietal cortex ( $-4\ -70\ 46$ ;  $-52\ -44\ 28$ ) and pulvinar thalamic nucleus ( $-14\ -32\ 14$ ).

mine whether they contributed to improved performance. A logistic regression showed that success significantly depended on span level, cue distance and the number of cue corner positions ( $P < 0.01$  for all tests). There was no significant interaction, however, between distance and day of training ( $P = 0.19$ ) nor between corners and day of training ( $P = 0.10$ ). Improved use of cue-dependent strategies could therefore not explain the increase in performance, which is consistent with the interviews.

### Experiment 2 - fMRI scanning

The subjects were scanned five times during training. fMRI data were analyzed in a random-effect analysis using task and working memory capacity as factors. Performance during scanning was used as a variable to define working memory capacity and the progression of training. Significant positive interactions were found in parietal and prefrontal cortices and in the thalamic and caudate nuclei (**Fig. 4a–d** and **Table 1**). Task-related activity in the frontal and parietal cortex for each scan is shown (**Fig. 3d**). Negative interactions were found in three regions (**Table 1**).

To confirm the findings, we carried out an additional analysis that did not include performance as a variable and thus was comparable to the analysis done in Experiment 1. This second analysis was based on subtraction images from each subject where mean activity that was related to working memory on scan 1 and 2 was subtracted from activity on scan 5. Values were extracted from the peak voxels in the regions in **Table 1**. All regions that were significant in the first analysis (except  $x\ y\ z$ , 46  $-78\ 34$ ; **Table 1**) also had significantly higher values in scan 5 as compared with scans 1 and 2 ( $P < 0.05$ ; paired  $t$ -test). A corresponding analysis of the decreases confirmed the findings in the first analysis (except  $x\ y\ z$ ,  $-52\ -16\ 34$ ).

### DISCUSSION

In the present study, we have investigated the effect of working memory training on brain activity. In Experiment 1, three subjects were scanned before and after training. In Experiment 2, eight subjects were scanned

five times during training. Each experiment confirmed the other by showing increased activity in prefrontal and parietal regions after working memory training (**Figs. 2** and **4**).

One difference between the experiments was that the prefrontal activation was in the left hemisphere in Experiment 2 but in the right in Experiment 1. With a less-conservative threshold in Experiment 2, however, a cluster of activation was evident in the right middle frontal gyrus (16 32 54;  $P = 0.21$ ). Moreover, we observed decreases in activity in the left postcentral gyrus and right inferior frontal sulcus in Experiment 2 but not in Experiment 1. Differences between the studies that may explain these inconsistencies are: (i) the inclusion of verbal working memory tasks in the training for Experiment 1; (ii) reproduction of the presented cues during scanning in Experiment 2 but only yes/no answers in Experiment 1; (iii) higher loads in the working memory tasks during scanning in Experiment 2 and (iv) additional scanning during training in Experiment 2. We suggest that the first difference listed above could explain the weaker generalization to nontrained tasks in Experiment 2.

Changes in accuracy during scanning could not explain changes in activity. In Experiment 1, only low-load trials were carried out in the scanner. This resulted in a ceiling effect and no significant changes in performance. Scanning in Experiment 2 included both high- and low-load trials, and the subjects improved significantly during training. Increases in prefrontal and parietal cortical activity were found in both experiments irrespective of these differences. Also, a decrease in activity in the cingulate sulcus was seen in both experiments. This could be related to a decreased need for motor planning that is associated with activity in this region. It is not probable that the decrease is related to less error-related activity<sup>15</sup>, because there was no decrease in error rate in Experiment 1.

**Table 1** Regions where brain activity changed after working memory training (Experiment 2)

Brain region	Hemisphere	Talairach coordinates			$t$	$P^a$	Cluster size (mm <sup>3</sup> )
		$x$	$y$	$z$			
<b>Increase in activity</b>							
Middle frontal gyrus	L	-26	22	56	7.03	0.000	4,024
Superior parietal cortex	L	-4	-70	46	5.83	0.011	2,408
Superior parietal cortex	L	-22	-46	76	5.82	0.002	3,232
Superior parietal cortex	R	14	-60	58	4.00	0.002	3,176
Intraparietal and inferior parietal cortex	L	-52	-44	28	4.84	0.000	4,456
Inferior parietal cortex	R	46	-78	34	4.52	0.006	2,720
Pulvinar thalamic nucleus	L	-14	-32	14	5.33	0.034	1,960
Caudate nucleus, head	R	10	8	12	5.00	0.013	2,352
<b>Decrease in activity</b>							
Cingulate sulcus	R	6	8	46	5.34	0.000	5,256
Inferior frontal sulcus	R	46	28	34	4.44	0.056	1,760
Postcentral gyrus	L	-52	-16	34	3.79	0.024	2,104

<sup>a</sup>Corrected for multiple comparisons.

The decrease in reaction time would presumably be associated with a shorter time on task and may explain some of the decreases in activity but could not explain the increases<sup>6</sup>.

Although we found increases in activity after training, several previous studies have found practice-related decreases in activity. When subjects are asked to generate a verb form of a noun, repeated presentation of the same noun results in decreased prefrontal and cingulate activity<sup>16</sup>. Experience-dependent decreases in activity also occur during long-term memory tasks<sup>17,18</sup> as well as motor tasks<sup>19,20</sup>. The effect of practicing these motor tasks was interpreted as an automation of performance, with less demand for control of attention. Several aspects differentiate between the practice of working memory tasks (and the related changes in brain activity) and the results in the studies mentioned above. In prior studies, training resulted in priming, encoding into long-term memory or automation, which in turn changed the task demands and the way the tasks were carried out during scanning. In working memory tasks with unique stimuli for each trial, the demand to keep information on line by active maintenance prevents automation<sup>21</sup>. Additionally, changes in activity occurred over a single scanning session in the studies mentioned. In the present study, changes occurred over several weeks, which is typically seen in skill acquisition and is suggested to be associated with cortical plasticity<sup>22,23</sup>. Consistent with this, a study of skill learning found that practicing the reading of mirror-reversed text for several days increased task-related brain activity<sup>24</sup>. Our finding that higher activity is associated with higher capacity is consistent with two previous studies that showed a positive correlation between cortical prefrontal activity and working memory capacity in children<sup>5,9</sup>. Additionally, a positive correlation exists between activity that is related to working memory and general fluid intelligence<sup>8</sup>, and MRI amplitude in a fronto-parietal network correlates with success on working memory tasks<sup>7,25</sup>.

In conclusion, we have shown that training-induced changes in working memory are associated with increases in task-related prefrontal and parietal activity. Cortical plasticity may underlie these signal changes. It is known that prefrontal association cortex involved in working memory is less stimulus specific than other parts of the cortex<sup>26,27</sup>. Improved function of a multimodal area could explain how training can affect different cognitive functions as suggested by previous studies<sup>14</sup> (T.K. *et al.*, unpublished data) and by the behavioral results in this study. Working memory includes several cognitive components such as encoding, control of attention, maintenance of information and resistance to interference. The specific functions of the areas where we observed training-induced increases in activity remain to be determined.

## METHODS

### Experiment 1

**Subjects.** Three male, right-handed volunteers (20–23 years of age) participated. Subjects had no history of psychiatric or neurological disease and gave written informed consent to participate in the study. The study was approved by the local ethics committee at the Karolinska Hospital.

**Procedure.** The subjects trained on three working memory tasks for 5 weeks and were scanned twice before and once after training. For pre- and post-training evaluation, a battery of neuropsychological tests was administered including the Span board task<sup>28</sup>, a visuo-spatial working memory task; Raven's Advanced Progressive Matrices<sup>29</sup>, a nonverbal reasoning task and the Stroop interference task (Dodrill's format)<sup>30</sup>, which measures response inhibition and impulsivity. Scanning included a working memory task and a control task in a block design.

**Working memory tasks used during scanning.** In Experiment 1, only low-load trials (five cues) were presented. The response phase (2,000 ms) followed

the cue presentation with a 1,000-ms delay. A probe circle with a number in it (1–5) appeared, and the task was to indicate whether the probe was in the same location as any of the cues and, if so, whether the number corresponded to the serial position of that cue. Responses were made by pressing on a response box with the index finger to indicate “yes” and with the middle finger to indicate “no”. In the control trial, a probe circle with the number 6 in it followed the cue presentation, and the subjects were asked to press a button when the probe appeared. The cues were presented using the E-prime software (Psychology Software Tools). Each block consisted of two working memory trials or two control trials. Each session contained 15 blocks, and there were four sessions per scan.

**Practiced working memory tasks.** Training included a visuo-spatial working memory task, a backwards digit span task and a letter span task. Difficulty was automatically adjusted to performance by changing the number of stimuli to be remembered. Each day of training included 30 trials of each task (35–45 min total).

**Magnetic resonance scanning.** Images were acquired using a 1.5 T GE Signa scanner. T2\*-weighted, gradient echo, spiral echo-planar images were acquired with TR = 2,500 ms, TE = 70 ms, flip angle = 85°, 22 axial slices, 5.0-mm slice thickness, 220 × 220-mm FOV, 64 × 64 grid, resulting in voxels that were 3.4 × 3.4 × 5.0 mm. Each session lasted 285 s and included acquisition of 240 volumes. Each scan included four sessions. T1-weighted spin echo images (FOV = 220 × 220 mm, 256 × 256 grid) were acquired in the same position as the functional images.

**Data analysis.** The data were analyzed with SPM99 (Wellcome Department of Cognitive Neurology, London, UK)<sup>31</sup>. Motion during scanning was estimated by six parameters (three translations, three rotations), which were used to realign the functional images to the first image in the series and were later used as confounds in the statistical analysis. The T1-weighted images were normalized to MNI305 space. The parameters from this normalization were then used to normalize the functional images, which were sampled to a voxel size of 3 × 3 × 3 mm and then smoothed with an isotropic Gaussian kernel of 6.0 mm. A threshold *t* value of 2.33 was used in all statistical analyses, and only clusters with a *P* < 0.05 after correction for multiple comparisons were considered statistically significant. The results from the fMRI scanning were used in a fixed-effect analysis. The training-induced increase was evaluated against variance that included nonspecific effects of being in the scanner. Scanning sessions 1, 2 and 3 were put into the same design matrix and were contrasted with each other using the contrast [−1 −1 2] for the three sessions. All behavioral *t*-tests were one-tailed.

### Experiment 2

**Subjects.** Eight healthy volunteers (29.3 ± 2.1 years of age; six females; one left handed) participated. Subjects had no history of psychiatric or neurological disease and gave written informed consent to participate in the study. The study was approved by the local ethics committee at the Karolinska Hospital.

**Procedure.** The subjects trained on three visuo-spatial working memory tasks for 5 weeks and were scanned five times during this period. Training effects on performance were evaluated with the Span board task and the Stroop interference task as described for Experiment 1 and the Digit span task<sup>32</sup>, a verbal working memory task. On day 1, subjects did the neuropsychological tests and undertook the first scan, which was the start of the working memory training. The following scans took place on days 2, 4, 8 and 23 of working memory training. The first two working memory training sessions were done in the scanner only and thus were not adaptive. Consequently, the subjects started the adaptive working memory training program on day 3. On each of the scanning days, the procedure for the scanning was identical and included a working memory task and a control task. The working memory trials were not, however, identical, in that the items to be recalled were randomly generated during each session. The working memory score from each scanning session was later used as an indicator of the training effect and was used as a variable in a random-effect analysis.

A questionnaire on strategies used and on changes in strategies was administered after the training. Additionally, a separate analysis on strategies was carried out on the training data to reveal aspects of stimuli that were used to

remember the cues<sup>33</sup>. This was done by measuring the impact on performance of (i) level (the number of stimuli in the trial) (ii) average geometric distance between stimuli (iii) number of 180° or 45° angles between successive cues (iv) number of intersections of an imaginary line drawn between cues (v) number of cues placed in corners and (vi) number of repetitions of previous positions, and by analyzing the interactions between these six factors and the day of training.

**Working memory tasks used during scanning.** The working memory task is explained (Fig. 1). Scanning was done as a block design alternating between working memory and control trials. Each scan consisted of four sessions including six control and six working memory trials, three of which were high load and three of which were low load, in random order.

**Practiced working memory tasks.** Three visuo-spatial working memory tasks were trained: Grid, Grid rotation and 3D Grid (Cogmed Cognitive Medical Systems). The tasks were based on the working memory task used in the scanner, but the number of cues in one sequence was adjusted to performance. The tasks were adjusted to performance and subjects were trained as described for Experiment 1.

**MR scanning.** The scanning procedure in Experiment 2 was similar to that in Experiment 1. Exceptions were: TE = 60 ms and 116 volumes were acquired in each session, lasting 288 s.

**Data analysis.** The procedure for data preprocessing in Experiment 2 was similar to that in Experiment 1. Exceptions were that functional images were normalized to a voxel size of 2 × 2 × 2 mm and a threshold of  $t > 2.44$  was used in the statistical analysis. All behavioral  $t$ -tests were one-tailed. For the statistical analysis, we calculated a subtraction image (working memory task minus control) that represented activity for each subject and day. This was done with a fixed-effect analysis where the  $\beta$ -values from the contrast in the general linear model represented differences in activity between the conditions. The subtraction images were then entered into a second-level random-effect analysis in which working memory capacity was used as the variable. Working memory capacity was calculated as the sum of the number of correctly recalled trials on level 7 multiplied by seven, and the number of correctly recalled trials on level 5 multiplied by five. Thus, this variable contained one score from each subject and scan. A regression analysis was done on the subtraction images from the first-level analysis to find areas where the blood oxygen level-dependent response values correlated with working memory capacity.

#### COMPETING INTERESTS STATEMENT

The authors declare competing financial interests (see the *Nature Neuroscience* website for details).

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