

Time Modulated Prefrontal and Parietal Activity during the Maintenance of Integrated Information as Revealed by Magnetoencephalography

Pablo Campo¹, Fernando Maestú^{1,2}, Tomás Ortiz^{1,3},
Almudena Capilla^{1,2}, Marta Santiuste¹, Alberto Fernández^{1,3}
and Carlos Amo¹

¹Centro de Magnetoencefalografía Dr Pérez-Modrego, Universidad Complutense de Madrid, Madrid, Spain, ²Departamento de Psicología Básica II (Procesos Cognitivos), Facultad de Psicología, Universidad Complutense de Madrid, Madrid, Spain and ³Departamento de Psiquiatría, Facultad de Medicina, Universidad Complutense de Madrid, Madrid, Spain

Using magnetoencephalography, we investigated the spatiotemporal patterns of brain magnetic activity responsible for maintaining verbal and spatial information in either an integrated or an unintegrated fashion. Considering time dimension, we noted a greater activation of a fronto-parietal network in early latencies during the maintenance of integrated information, and a different pattern during the maintenance of unintegrated material, showing a greater activation in a fronto-posterior network in late latencies. The greater activation found in certain areas which are traditionally reported as being engaged in spatial working memory (i.e. superior frontal gyri, dorsolateral prefrontal cortex, superior and inferior parietal lobes) when subjects maintained integrated information could be explained by a greater weight of the spatial dimension. It is as if words somehow acquired a spatial attribute, thus exerting a greater load in a neural network specialized in spatial working memory. Alternatively, and not mutually exclusive, we also propose that during the maintenance of integrated information the allocation of cognitive resources is less interfering than during the maintenance of unintegrated information, making it easier.

Keywords: fronto-parietal circuits, functional brain imaging, neural networks, spatial working memory, verbal working memory

Introduction

Working memory (WM) is considered the ability to temporarily maintain and manipulate an active representation of information. Baddeley and Hitch (1974) proposed a highly influential model which postulates a multicomponent system with two subsidiary systems involved in the maintenance of verbal and visuospatial information respectively, which are coordinated by a central executive system.

Sustained neural activity over memory retention intervals in delayed tasks is generally interpreted as the neural basis of working memory (Chafee and Goldman-Rakic, 1998). Evidence from studies with non-human primates as well as in humans shows that working memory task performance requires the activation of multiple widely distributed regions in posterior perceptual areas, motor cortices, and prefrontal cortex. The extent to which these areas are activated largely depends on the requirements of the working memory task (D'Esposito *et al.*, 1999).

Maintenance is considered as a process of keeping information in mind in the absence of external stimuli and corresponds to the mnemonic aspect of the WM. On the other hand, manipulation refers to the reorganization of the information that is being maintained and it is supposed to be supported by the hypothetical central executive system.

Two basic processes are assumed to be involved in the active maintenance of information: storage of material and rehearsal of

material. Neuropsychological and neuroimaging evidence indicated a significant contribution of the posterior brain regions in the passive storage of information, while more anteriorly located brain areas, such as the premotor cortex, would be involved in the rehearsal of the material (for reviews, see Cabeza and Nyberg, 2000; Fletcher and Henson, 2001).

Although the model proposed by Baddeley and Hitch (1974) successfully explains neuropsychological and developmental data from normal and impaired persons, it leaves several phenomena unanswered. In order to fill this gap, Baddeley (2000) has recently revised his model of working memory postulating a new storage subsystem: the episodic buffer. This new component constitutes an interface between the phonological and visuo-spatial subsystems of the working memory and long-term memory. The main assumption is that the episodic buffer is capable of integrating information from a variety of sources. A functional magnetic resonance imaging (fMRI) study by Prabhakaran *et al.* (2000) has tested this model. Participants performed two different tasks in which they had to maintain verbal (letters) and spatial (locations) information either in an integrated or in an unintegrated manner. Although many brain regions were activated in both conditions, including frontal, parietal and temporal areas, the authors found greater activation in the right prefrontal cortex (specifically right middle and superior frontal gyri) when the participants had to maintain integrated information (spatial and verbal information) than when they maintained unintegrated information.

Encouraged by these results, we used magnetoencephalography (MEG) to investigate the spatiotemporal patterns that characterized the maintenance of integrated information. MEG is known to provide detailed information of brain activity with milliseconds accuracy, which seems appropriate for elucidating the neural substrates of working memory processes.

Materials and Methods

Participants

After signing a consent form, 11 right-handed native Spanish speakers (six females and five males, ranging in age between 24 to 36 years; mean = 28.18, SD = 4.24) participated in the study. Participants were interviewed and entered in the study if they met the following inclusion criteria: (i) absence of a previous history of neuropathological conditions; (ii) absence of prior hospitalization due to psychopathological diseases (e.g. schizophrenia, major depression); (iii) absence of a previous history of abnormal psychomotor development; (iv) no antecedent of drug or alcohol abuse; (v) no psychotropic medication use in amounts that could affect concentration, attention, or produce somnolence; and (vi) Spanish being the primary language.

Stimuli and Tasks

MEG scans were obtained during two experimental tasks: the Bound task (integrated information) and the Separate task (unintegrated

information). For counterbalancing purposes the order of presentation of the tasks was controlled. Thus, six participants performed the Bound task first and five performed the Separate task first. Each participant completed both experimental tasks during a single recorded session, lasting 40 min.

In both conditions participants viewed for 3 s a stimulus array comprising four words and four ellipses and were asked to remember the words and the locations of the ellipses. In the Bound task (Fig. 1), words were placed within the ellipses, while in the Separate task (Fig. 2), words were located centrally in the display. Ellipses were

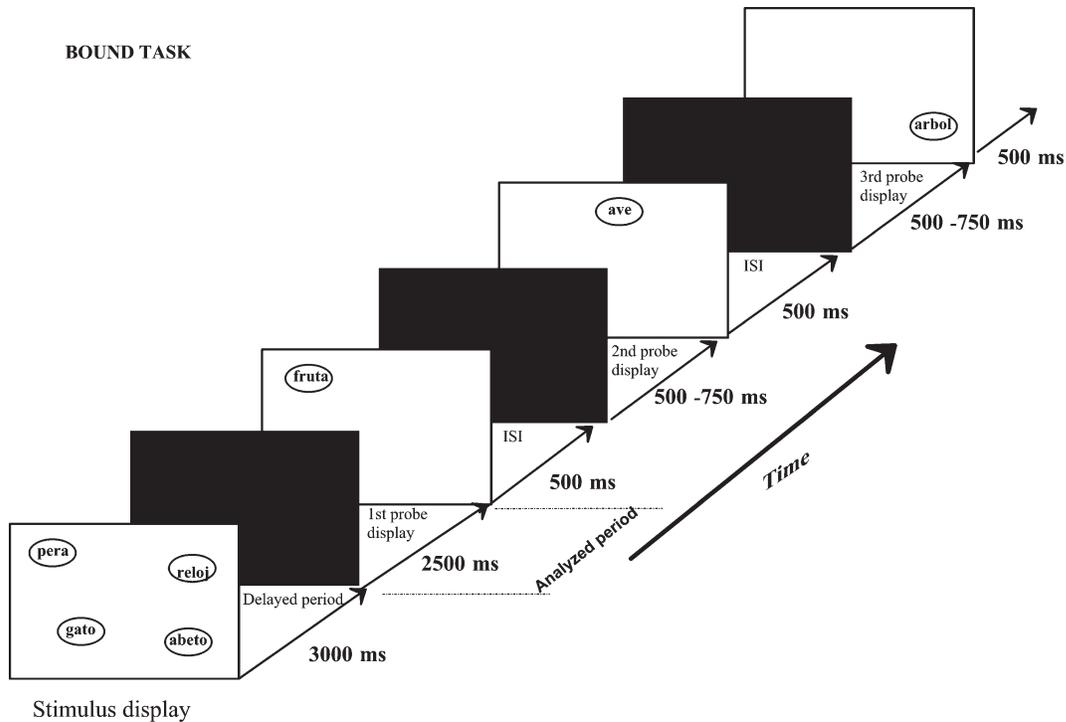


Figure 1. Schematic of the bound condition trial type. The Spanish words within the ellipses mean: ‘pear’, ‘clock’, ‘cat’, ‘fir’ (Stimulus display); ‘fruit’ (1st probe display); ‘bird’ (2nd probe display); ‘tree’ (3rd probe display).

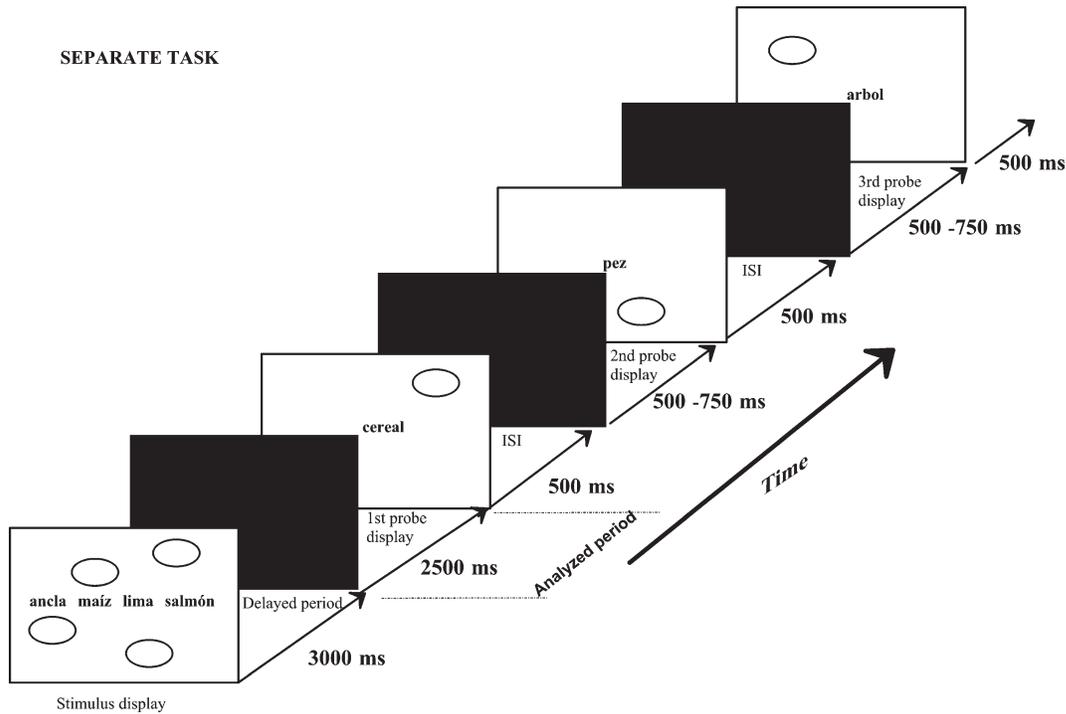


Figure 2. Schematic of the separate condition trial type. The Spanish words means: ‘anchor’, ‘corn’, ‘lime’, ‘salmon’ (Stimulus display); ‘cereal’ (first probe display); ‘fish’ (second probe display); ‘tree’ (third probe display).

located randomly in both conditions. Participants had to maintain both types of information for 2500 ms. Subsequently, they were presented three consecutive probe displays comprising a word, which was a semantic category, and one ellipse. Participants had 500 ms for each probe to decide if one of the words in the stimulus display belonged to the semantic category represented by the word in the probe display and whether the ellipse was in the same location as one of the ellipses of the stimulus display (Fig. 1). There was an interval between probe displays of random duration (between 500 and 700 ms). Participants should answer affirmatively only when both word and location had been presented in the stimulus display.

The stimuli were projected through a LCD video-projector (VPL-X600E; Sony), situated outside the shielded room on to a series in-room mirrors, the last of which was suspended ~1 m above the subject's face. The stimuli subtended 1.8° and 3° of horizontal and vertical visual angle, respectively.

Data Collection and Analysis

We only analyzed the delay period between the end of the stimulus display and the onset of the first probe display, since delay-period activity is considered 'one of the best candidates for a critical neural correlate of working memory' (Chafee and Goldman-Rakic, 1998). Consequently, the processes of encoding or retrieval were not analyzed, but only the temporary maintenance of verbal and spatial information.

MEG recordings were made with a whole-head neuromagnetometer (Magnes 2500®; 4-D Neuroimaging Inc., San Diego, CA) consisting of 148 magnetometer coils. The instrument is housed in a magnetically shielded room designed to reduce environmental magnetic noise that might interfere with biological signals. The signal was filtered online with a band pass between 0.1 and 50 Hz, digitized for 5500 ms (254 Hz sampling rate) including a 150 ms prestimulus period, and subjected to an adaptive filtering procedure that is part of the 4-D Neuroimaging signal analysis package. The single trial event-related fields (ERFs) were then averaged together after removing those during which an eye movement or blink had occurred. For this purpose electro-oculogram monitoring was conducted, and all epochs coinciding with blinks and eye movements were rejected, as indicated by a peak to peak amplitude in the electro-oculogram channel > 50 μ V. A minimum of 90 ERF epochs were collected to calculate each averaged waveform. Finally, the averaged epochs were digitally filtered with a low pass 20 Hz filter.

The intracranial generators of the observed ERFs (henceforth referred to as 'activity sources') were modeled as single equivalent current dipoles (ECDs) and fitted at successive 4 ms intervals by using the nonlinear Levenberg-Marquardt algorithm. Regions of interest are not established a priori in MEG studies. Modeling of activity sources is performed solely on the basis of the surface distribution of magnetic flux without making hypotheses or placing constraints regarding the anatomical location of the underlying intracranial sources. The resulting individual distribution of magnetic flux are inspected visually (and blindly with respect to experimental condition). For a given point in time, the ECD fitting algorithm was applied to the magnetic flux measurements obtained from a group of 34–38 magnetometers, always including both magnetic flux extremes. The algorithm used in this study searched for the ECD that was most likely to have produced the observed magnetic field distribution at a given point in time. The ECD solutions were considered satisfactory after meeting the following criteria: (i) correlation coefficient of at least 0.9 between the observed and the 'best' predicted magnetic field distribution, (ii) a goodness of fit of at least 0.9 or higher and (iii) a confidence volume < 5 cm³. We elected this method because its concurrent validity has been successfully tested in comparison with the results of invasive brain mapping techniques in patient series (Breier *et al.*, 1999; Papanicolaou *et al.*, 1999; Maestú *et al.*, 2001; Simos *et al.*, 2002).

In order to determine the anatomical regions where the activity sources were located, ECD coordinates were overlaid onto T_1 -weight, magnetic resonance (MR) images ($T_R = 13.6$ ms, $T_E = 4.8$ ms, recording matrix 256 \times 256 pixels, 1 excitation, 240 mm field of view, 1.4 mm slice thickness) obtained from every participant on a separate session. The MEG-MRI overlay was performed using the STAR program, which is part of the 4-D Neuroimaging software (for a detailed description of the co-registration process, see Maestú *et al.*, 2002). Visual inspection of the

resulting activation profiles showed that activity sources were computed consistently across participants (i.e. 80% of the participants, binomial test $P < 0.035$) in the following areas: inferior prefrontal cortex (IFG), encompassing ventrolateral prefrontal cortex (VLPFC, BA 47/11) and pars triangularis (BA 45); dorsolateral prefrontal cortex (DLPFC, BA 9/46); superior frontal gyrus (SFG, BA 8); premotor cortex and supplementary motor area (PM/SMA, BA 6); superior parietal lobe (SPL, BA 7); inferior parietal lobe (IPL, BA 39/40); superior temporal gyrus (STG, BA 22/42); and inferior/middle temporal gyrus (ITG, BA 20/21/37).

The temporal course of regional activation was examined by placing activity sources in each area through eight separate 300-ms latency windows and one 100 ms latency window (the last 100 ms.) covering the entire delay period (2500 ms).

Results

Behavioral Data

The analyses of the performance across tasks revealed that participants were more accurate in the bound (60.99 %) than in the separate (54.80 %) condition ($t = 5.61$, $df = 10$, $P < 0.05$). These results indicate that the Separate task was more difficult than the Bound task.

Statistical Analysis

A repeated measures analysis of variance, with Task and Hemisphere as the within-subject factors, was conducted in order to compare the number of activity sources over each of the areas indicated above between tasks. The results were evaluated using the Huynh-Feldt method as a precaution against the threat posed by inhomogeneities of variance among cell means. If there were a significant main effect or interaction ($P < 0.05$), a *post hoc* analysis was performed using the Bonferroni correction for multiple comparisons.

Spatiotemporal Activation Profiles

First Time Window: 0–300 ms

There was a significant effect of Task on SFG [$F(1,10) = 8.02$, $P < 0.05$] and on SPL [$F(1,10) = 6.87$, $P < 0.05$]. Further analyses indicated that both areas were more activated in the Bound task in comparison to the Separate task.

A main effect of Hemisphere on DLPFC [$F(1,10) = 6.33$, $P < 0.05$] indicated that the right hemisphere was more activated across tasks than the left hemisphere.

A Task \times Hemisphere interaction was found on IFG [$F(1,10) = 5.63$, $P < 0.05$]. Follow-up analyses showed a greater activation of the right IFG in the Separate task in comparison to the Bound task (Fig. 3A).

Second Time Window: 300–600 ms

A main effect of Task was found on SFG [$F(1,10) = 6.17$, $P < 0.05$]. Results showed greater activation of this area in the Bound task than in the Separate task. A significant Task \times Hemisphere interaction on STG [$F(1,10) = 6.27$, $P < 0.05$] indicated that the right STG showed a greater number of activity sources in the Bound task (Fig. 3B).

Third Time Window: 600–900 ms

A main effect of Hemisphere on ITL revealed that the left hemisphere was more activated than the right hemisphere across task conditions [$F(1,10) = 10.67$, $P < 0.05$].

A Task \times Hemisphere interaction [$F(1,10) = 5.63$, $P < 0.05$] indicated that the right IPL was more activated in the Bound task than in the Separate task (Fig. 4A).

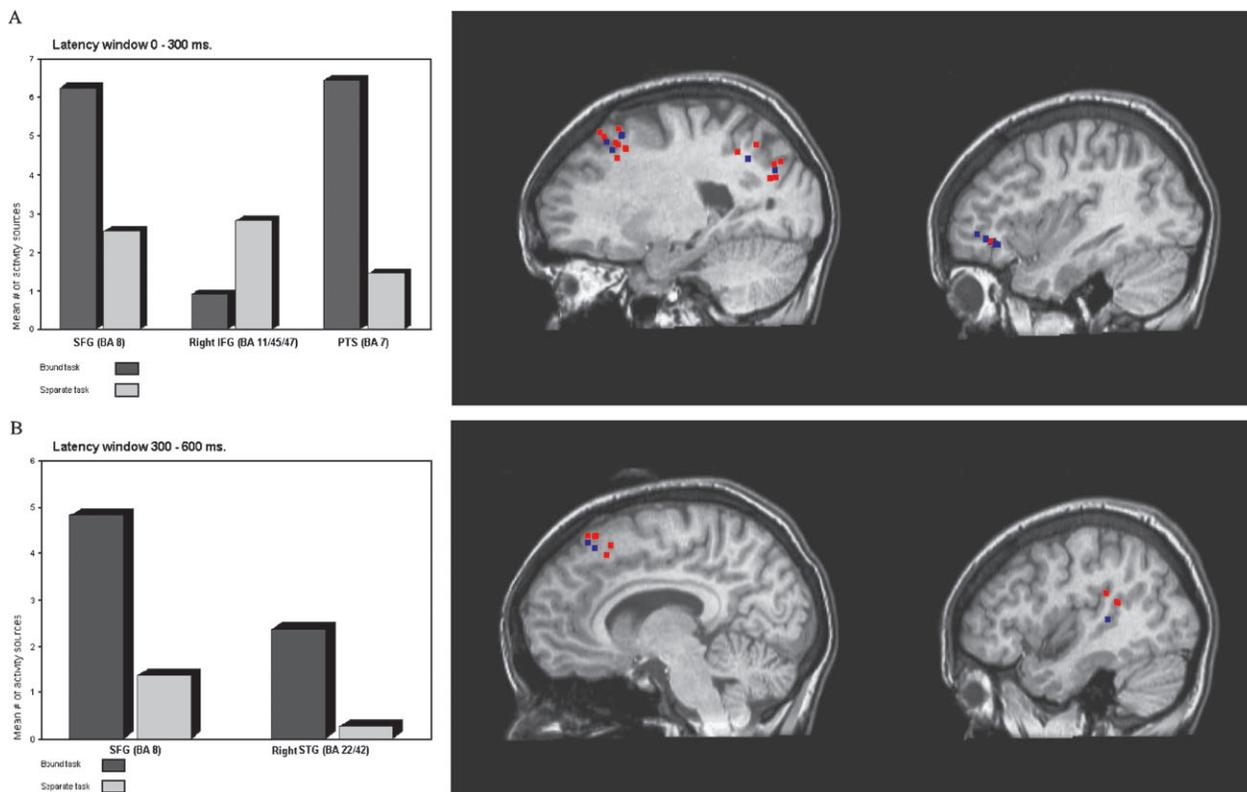


Figure 3. Graphs and maps of the amount of activation in terms of number of activity sources for a prototypical subject. Activity in the Bound task is coded in red and activity in the Separate task is coded in blue on the MRIs. (A) Graph and maps for the latency window between 0 and 300 ms. (B) Graph and maps for the latency window between 300 and 600 ms.

Fourth Time Window: 900–1200 ms

The ANOVA yielded a main effect of Task on DLPFC [$F(1,10) = 10.47, P < 0.05$]. This effect was accounted for a greater number of activity sources in the Bound task than in the Separate task.

A Task \times Hemisphere interaction was also found for IPL [$F(1,10) = 6.21, P < 0.05$]. Further analyses showed a greater activation in the right IPL in the Bound task in comparison to Separate task (Fig. 4B).

Fifth Time Window: 1200–1500 ms

A main effect of Hemisphere on DLPFC [$F(1,10) = 5.71, P < 0.05$] indicated that the right hemisphere was more activated than the left hemisphere across tasks.

Seventh Time Window: 1800–2100 ms

A main effect of Task on STG indicated that this area was more activated in the Separate task than in the Bound task [$F(1,10) = 17.50, P < 0.05$; Fig. 4C).

Discussion

In the current study we investigated whether the maintenance of integrated and unintegrated material (words and locations) is supported by different neural systems. Both tasks activated similar and widely distributed areas which according to previous reports are engaged in verbal and spatial working memory tasks (Courtney *et al.*, 1998; Owen *et al.*, 1998; Smith and Jonides, 1998; Becker *et al.*, 1999; Postle and D'Esposito, 1999; Henson *et al.*, 2000; Rama *et al.*, 2001). These areas included: inferior prefrontal cortex (IFG), encompassing ventrolateral

prefrontal cortex (VLPFC, BA 47/11) and pars triangularis (BA 45); dorsolateral prefrontal cortex (DLPFC, BA 9/46); superior frontal gyri (SFG, BA 8); premotor cortex and supplementary motor area (PM/SMA, BA 6); anterior cingulate cortex (ACC, BA 24/32); superior parietal lobe (SPL, BA 7); inferior parietal lobe (IPL, BA 39/40); superior temporal gyrus (STG, BA 22/42); and inferior/middle temporal lobe (ITL, BA 20/21/37).

Taking advantage of MEG's time resolution, we investigated the latencies at which different brain areas were activated during the maintenance of integrated and unintegrated information. We observed that while both tasks activated identical brain regions across the retention period, the extent of activation significantly differed depending on the time period of analysis. Thus, early in the delay period, a greater activation of the SFG and the SPL (latency window between zero and 300 ms) and of the SFG and right STG (latency window between 300–600 ms) was found when subjects maintained integrated information. Courtney and colleagues (Courtney *et al.*, 1998; Haxby *et al.*, 2000; Sala *et al.*, 2003) have proposed a specialized role for area 8 (in SFG) in spatial working memory. These results have been replicated by other authors using different neuroimaging techniques (Carlson *et al.*, 1998; Rypma *et al.*, 1999; Thomas *et al.*, 1999; Zarahn *et al.*, 1999; Pollmann and von Cramon, 2000; Postle *et al.*, 2000; Rowe *et al.*, 2000; Gruber, 2001; Gruber and von Cramon, 2001; Rowe and Passingham, 2001; Glahn *et al.*, 2002; Sakai *et al.*, 2002; Zurovski *et al.*, 2002), pointing to area 8 as playing a key role in the maintenance of spatial information. On the other hand, the activation of the superior parietal lobe in spatial working memory tasks has been well established in a great amount of studies (Chafee and Goldman-Rakic, 1998; Coull and Frith, 1998;

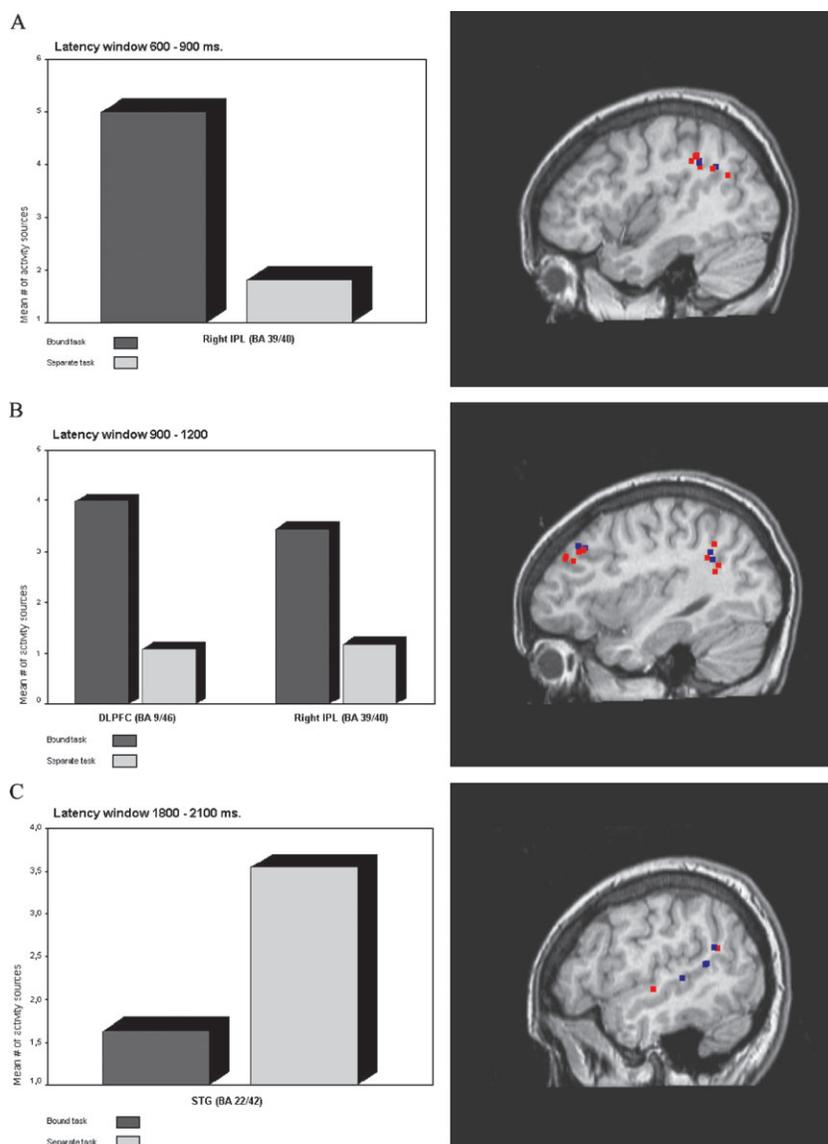


Figure 4. Graphs and maps of the amount of activation in terms of number of activity sources for a prototypical subject. Activity in the Bound task is coded in red and activity in the Separate task is coded in blue on the MRIs. (A) Graph and maps for the latency window between 600 and 900 ms. (B) Graph and maps for the latency window between 900 and 1200 ms. (C) Graph and maps for the latency window between 1800 and 2100 ms. Only latency windows in which there were differences between experimental conditions are depicted.

Smith and Jonides, 1998; Awh *et al.*, 2000; Fletcher and Henson, 2001; Glahn *et al.*, 2002). The anatomical connectivity between SFG and SPL has been reported in several studies (Petrides and Pandya, 1999; Petrides, 2000b). Furthermore, several papers have demonstrated a conjoint activation of both areas during the performance of spatial working memory tasks (Carlson *et al.*, 1998; Okada and Salenius, 1998; Haxby *et al.*, 2000; Glahn *et al.*, 2002; Munk *et al.*, 2002; Passingham and Rowe, 2002; Zurovski *et al.*, 2002). In addition, evidence derived from experiments with non-human primates have shown that most of the cells firing during the retention period in spatial working memory tasks are located in area 8A and the convexity of area 8 as well as in the superior parietal lobe (Chafee and Goldman-Rakic, 1998). Concerning the right-sided STG activation, Corbetta *et al.* (2002) have recently shown a specific response of this area during the delay period of a spatial working memory task.

In the following 600 ms (600–900 and 900–1200 ms latency windows) a greater activation of the right IPL was observed during the maintenance of integrated information. Recently, Munk *et al.* (2002) have found a predominant activation of the right IPL during a spatial working memory task as compared to a visual working memory task. These results suggest that a sustained greater activation of this network during the early phase of the retention period is critical for the maintenance of integrated information. Premotor cortex and SMA were highly activated during these time periods in both tasks. Since maintaining information includes storage and rehearsal, the activation of premotor cortices could be due to the need of refreshing the material storage in posterior perceptual areas (Paulesu *et al.*, 1993; Vallar *et al.*, 1997; Okada and Salenius, 1998; Smith and Jonides, 1998; Henson *et al.*, 2000). These data are in line with previous results supporting a model of attention-based rehearsal

in which an interactive frontal and parietal network mediates the 'allocation of spatial attention to locations that are held in working memory' (Corbetta, 1998; LaBar *et al.*, 1999; Awh *et al.*, 2000; Nobre *et al.*, 2000; Awh and Jonides, 2001). Similar results have been reported for verbal material, with frontal areas refreshing the information that is stored in posterior brain regions, mainly in the inferior parietal lobe (Paulesu *et al.*, 1993; Petrides *et al.*, 1993; Jonides *et al.*, 1998; Becker *et al.*, 1999; Henson *et al.*, 2000).

Taking into account these previous results, we interpreted our findings as indicative of a greater activation of a neural network specialized in spatial working memory when subjects maintained integrated information. This fact could be explained by a greater weight of the spatial dimension in the bound task in comparison to the separate task. It seems as if when words are integrated into locations, the former acquire spatial attributes.

An alternative explanation resides in the observation that locating words into ellipses produced less interference between cognitive resources, thus facilitating the processing of both dimensions (see Garavan *et al.*, 2000).

The greater activation of the right IFG noted during the maintenance of unintegrated information in the first latency window (0–300 ms.), would suggest a stronger engagement of the verbal maintenance process in the Separate task. Bilateral activation of IFG has been related with phonological and semantic working memory in several studies (Braver *et al.*, 1997; Gabrieli *et al.*, 1998; Poldrack *et al.*, 1999; Wiggs *et al.*, 1999; Passingham *et al.*, 2000; Clark and Wagner, 2003; Hoshi *et al.*, 2003; Veltman *et al.*, 2003). Considering that the tasks in our study required the maintenance of words and that most participants reported that they generated semantic category candidates to match the words during the delay period, an engagement of a semantic neural system is very likely. Although speculative, this greater activity could indicate that participants placed greater demands on the semantic working memory system in the Separate task, maintaining words on-line first, and subsequently engaging the spatial working memory system. Differing from the Bound task, trying to maintain both types of materials (verbal and spatial) when they are presented in a separate manner is more interfering, implying that both processes compete for cognitive resources.

The greater activation of the left middle/inferior temporal cortex in both conditions (600–900 ms.) appears to be related to the semantic processing demanded by the task. Several studies (Crosson *et al.*, 1999; Maestú *et al.*, 2003) have found activity increases in the dominant ventral temporal cortex during semantic memory tasks. This area has also been identified as participating in semantic processing (for a review, see Cabeza and Nyberg, 2000).

Another brain region that showed distinctive activation during the maintenance of integrated information was the DLPFC (900–1200 ms). This area also showed a right preponderance in both tasks in two different time windows (0–300 and 1200–1500 ms). Considering that DLPFC has been associated either with spatial maintenance (Goldman-Rakic, 1994, 1995) or with the manipulation of the information held in mind (Petrides, 1995, 2000a), two processes which are likely involved in the current tasks, the role played by this area remains undetermined.

It was not until later in time that a new increase in the activation of an area occurred during the maintenance of unintegrated information. During the period between 1800 and

2100 ms, the STG was bilaterally more activated in the Separate task in comparison to the Bound task. Bilateral activation of the STG has been demonstrated in studies of verbal and spatial working memory, although more consistently in the former (Paulesu *et al.*, 1993; Wiggs *et al.*, 1999; Cabeza and Nyberg, 2000; Henson *et al.*, 2000; Corbetta *et al.*, 2002; Zurowski *et al.*, 2002; Clark and Wagner, 2003). This area is conceptualized as being involved in perception and phonological processing of verbal stimuli (Paulesu *et al.*, 1993; Smith and Jonides, 1998; Zurowski *et al.*, 2002).

To the best of our knowledge, there is only one previous neuroimaging study investigating the maintenance of integrated versus unintegrated information using a working memory paradigm (Prabhakaran *et al.*, 2000). These authors pointed out that, while the same regions were activated in both conditions, including frontal, parietal and temporal areas, there was a greater activation of right prefrontal cortex (specifically right middle and superior frontal gyri) when subjects maintained integrated information. Conversely, a greater activity was found in posterior regions (bilateral parietal and temporal areas) when subjects maintained unintegrated information.

Although our results partially replicate the findings reported by Prabhakaran *et al.* (2000), some differences were also found. We converge with these authors in finding greater activation of prefrontal areas (SFG and DLPFC), although bilaterally, when subjects maintained integrated information. Current results also agree with those of Prabhakaran *et al.* (2000) in showing a greater bilateral activation of the STG when subjects maintained unintegrated information. Contrary to what these authors reported, we found a greater activation of superior and right inferior parietal lobes in the bound task in certain latency windows. The observed discrepancies could be explained by two hypotheses. First, the difference in the type of material that we presented in our study, words instead of letters, could be interpreted as the root for the divergence found between studies. Although not very consistently, it has been argued that subjects may rely more on semantic codes to retain words in working memory instead of a phonological code, with the 'latter implicating posterior parietal mechanisms and the former other brain regions' (Jonides *et al.*, 1998). However, the greater number of activity sources found over parietal areas in the bound task compared to the separate task in our study cannot be explained solely by the differences in the type of material presented, since we asked participants to maintain words in both task conditions and therefore this should have affected both of them. Recently, Crosson *et al.* (1999) have compared semantic, phonological and orthographical working memory tasks using fMRI and found few significant differences among them regarding activation of posterior areas (see also Clark and Wagner, 2003). Thus, the greater activation of parietal cortices in the bound task could not be explained by the fact that words were presented instead of letters.

An alternative explanation of the observed discrepancies could be the block design method of analysis used in the above-mentioned study. This approach does not allow to accurately segregate the different stages of a working memory task (encoding, maintenance and retrieval), added to a temporal resolution in the range of seconds, which limits the capability of providing accurate information on the timing of neural processing. By using a single trial method of analysis we could focus on a specific phase (i.e. maintenance period) independently of others (i.e. encoding and retrieval) with an accuracy of

milliseconds. Probably, our data would be better compared with those of a study using a high temporal resolution technique, as could be event related fMRI.

Another disparity between studies was the activation of the IFG found in the current investigation. We considered IFG activation as being related to the semantic processing elicited by the demands of our tasks. This area has been specifically linked to semantic memory in several studies (for a review, see Poldrack *et al.*, 1999). In addition, the fact that Prabhakaran *et al.* (2000) did not report activation in this area further support this interpretation.

In summary, we consider that the activation of a neural network encompassing frontal and posterior brain regions supports the maintenance of integrated and unintegrated material, since the same regions were activated during both tasks. However, the greater activation found in certain areas traditionally reported as being engaged in spatial working memory, (i.e. SFG, DLPFC, SPL and IPL) during the maintenance of integrated information could be explained by a greater weight of the spatial dimension in this task. It is as if words could somehow acquire spatial attributes, thus placing a greater load in a neural network specialized in spatial working memory. It should be noted that these differences are modulated by time, with greater activation at early latencies occurring in the Bound task, and greater activation of posterior cortices during later latencies in the Separate task. Complementing this interpretation of the data, we tentatively suggest that during maintenance of integrated information, the allocation of cognitive resources is less interfering than during the maintenance of unintegrated information, making it easier, as the behavioural results indicate.

These results highlight the benefit of using neuroimaging techniques that provide high temporal resolution, allowing measures of brain activity with milliseconds accuracy. Although our findings, as well as those of Prabhakaran *et al.* (2000), lead to the conclusion that prefrontal cortex is a key structure for integrating information, we consider that the time modulated prefronto-posterior interaction is the mean by which this integration is accomplished. As has been outlined by other authors (Haxby *et al.*, 2000), 'sustained activity during memory delays is not restricted to a single prefrontal working memory area, but, rather, is a broadly distributed function', in other words, a neural network encompassing temporal, parietal and frontal areas.

However, based on current results, we can not determine if there is a separate store for integrating information, or if the integration is based on the recruitment of different neural networks supporting working memory. Further investigation of how frontal and posterior areas interact during the maintenance of either integrated or unintegrated information of different modalities (i.e. shapes and colours) should be conducted in forthcoming studies.

Notes

Address correspondence to Tomás Ortiz, Centro de Magnetoencefalografía Dr Pérez-Modrego, Pabellón 8, Facultad de Medicina, Universidad Complutense de Madrid, 28040 Madrid, Spain. Email: cmeg@rect.ucm.es.

References

Awh E, Jonides J (2001) Overlapping mechanisms of attention and spatial working memory. *Trends Cogn Sci* 5:119-126.

- Awh E, Anillo-Vento L, Hillyard SA (2000) The role of spatial selective attention in working memory for locations: evidence from event-related potentials. *J Cogn Neurosci* 12:840-847.
- Baddeley A (2000) The episodic buffer: a new component of working memory. *Trends Cogn Neurosci* 4:417-423.
- Baddeley A, Hitch G (1974) Working memory. New York: Academic Press.
- Becker JT, MacAndrew DK, Fiez JA (1999) A comment on the functional localization of the phonological storage subsystem of working memory. *Brain Cogn* 41:27-38.
- Braver TS, Cohen JD, Nystrom LE, Jonides J, Smith EE, Noll DC (1997) A parametric study of prefrontal cortex involvement in human working memory. *Neuroimage* 5:49-62.
- Breier JL, Simos PG, Zouridakis G, Papanicolaou AC (1999) Temporal course of regional brain activation associated with phonological decoding. *J Clin Exp Neuropsychol* 21:465-476.
- Cabeza R, Nyberg L (2000) Imaging cognition II: an empirical review of 275 PET and fMRI studies. *J Cogn Neurosci* 12:1-47.
- Carlson S, Martinkauppi S, Rama P, Salli E, Korvenoja A, Aronen HJ (1998) Distribution of cortical activation during visuospatial *n*-back tasks as revealed by functional magnetic resonance imaging. *Cereb Cortex* 8:743-752.
- Chafee MV, Goldman-Rakic PS (1998) Matching patterns of activity in primate prefrontal area 8a and parietal area 7ip neurons during a spatial working memory task. *J Neurophysiol* 79:2919-2940.
- Clark D, Wagner AD (2003) Assembling and encoding word representations: fMRI subsequent memory effects implicate a role for phonological control. *Neuropsychologia* 41:304-317.
- Corbetta M (1998) Frontoparietal cortical networks for directing attention and the eye to visual locations: identical, independent, or overlapping neural systems? *Proc Natl Acad Sci USA* 95:831-838.
- Corbetta M, Kincade JM, Shulman GL (2002) Neural systems for visual orienting and their relationships to spatial working memory. *J Cogn Neurosci* 14:508-523.
- Coull JT, Frith CD (1998) Differential activation of right superior parietal cortex and intraparietal sulcus by spatial and nonspatial attention. *Neuroimage* 8:176-187.
- Courtney SM, Petit L, Maisog JM, Ungerleider LG, Haxby JV (1998) An area specialized for spatial working memory in human frontal cortex. *Science* 279:1347-1351.
- Crosson B, Rao SM, Woodley SJ, Rosen AC, Bobholz JA, Mayer A, Cunningham JM, Hammeke TA, Fuller SA, Binder JR, Cox RW, Stein EA (1999) Mapping of semantic, phonological, and orthographic verbal working memory in normal adults with functional magnetic resonance imaging. *Neuropsychology* 13:171-187.
- D'Esposito M, Postle BR, Ballard D, Lease J (1999) Maintenance versus manipulation of information held in working memory: an event-related fMRI study. *Brain Cogn* 41:66-86.
- Fletcher PC, Henson RN (2001) Frontal lobes and human memory: insights from functional neuroimaging. *Brain* 124:849-881.
- Gabrieli JD, Poldrack RA, Desmond JE (1998) The role of left prefrontal cortex in language and memory. *Proc Natl Acad Sci USA* 95:906-913.
- Garavan H, Ross TJ, Li SJ, Stein EA (2000) A parametric manipulation of central executive functioning. *Cereb Cortex* 10:585-592.
- Glahn DC, Kim J, Cohen MS, Poutanen VP, Therman S, Bava S, Van Erp TG, Manninen M, Huttunen M, Lonnqvist J, Standertskjold-Nordenstam CG, Cannon TD (2002) Maintenance and manipulation in spatial working memory: dissociations in the prefrontal cortex. *Neuroimage* 17:201-213.
- Goldman-Rakic PS (1994) The issue of memory in the study of prefrontal functions. Berlin: Springer.
- Goldman-Rakic PS (1995) Architecture of the prefrontal cortex and the central executive. *Ann N Y Acad Sci* 769:71-83.
- Gruber O (2001) Effects of domain-specific interference on brain activation associated with verbal working memory task performance. *Cereb Cortex* 11:1047-1055.
- Gruber O, von Cramon DY (2001) Domain-specific distribution of working memory processes along human prefrontal and parietal cortices: a functional magnetic resonance imaging study. *Neurosci Lett* 297:29-32.

- Haxby JV, Petit L, Ungerleider LG, Courtney SM (2000) Distinguishing the functional roles of multiple regions in distributed neural systems for visual working memory. *Neuroimage* 11:380-391.
- Henson RN, Burgess N, Frith CD (2000) Recoding, storage, rehearsal and grouping in verbal short-term memory: an fMRI study. *Neuropsychologia* 38:426-440.
- Hoshi Y, Tsou BH, Billock VA, Tanosaki M, Iguchi Y, Shimada M, Shinba T, Yamada Y, Oda I (2003) Spatiotemporal characteristics of hemodynamic changes in the human lateral prefrontal cortex during working memory tasks. *Neuroimage* 20:1493-1504.
- Jonides J, Schumacher EH, Smith EE, Koeppel RA, Awh E, Reuter-Lorenz PA, Marshuetz C, Willis CR (1998) The role of parietal cortex in verbal working memory. *J Neurosci* 18:5026-5034.
- LaBar KS, Gitelman DR, Parrish TB, Mesulam M (1999) Neuroanatomic overlap of working memory and spatial attention networks: a functional MRI comparison within subjects. *Neuroimage* 10:695-704.
- Maestú F, Fernandez A, Simos PG, Gil-Gregorio P, Amo C, Rodriguez R, Arrazola J, Ortiz T (2001). Spatio-temporal patterns of brain magnetic activity during a memory task in Alzheimer's disease. *Neuroreport* 12:3917-3922.
- Maestú F, Ortiz T, Fernandez A, Amo C, Martin P, Fernandez S, Sola RG (2002) Spanish language mapping using MEG: a validation study. *Neuroimage* 17:1579-1586.
- Maestú F, Simos PG, Campo P, Fernandez A, Amo C, Paul N, Gonzalez-Marqués J, Ortiz T (2003) Modulation of brain magnetic activity by different learning strategies. *Neuroimage* 20:110-121.
- Munk MH, Linden DE, Muckli L, Lanfermann H, Zanella FE, Singer W, Goebel R (2002) Distributed cortical systems in visual short-term memory revealed by event-related functional magnetic resonance imaging. *Cereb Cortex* 12:866-876.
- Nobre AC, Gitelman DR, Dias EC, Mesulam MM (2000) Covert visual spatial orienting and saccades: overlapping neural systems. *Neuroimage* 11:210-216.
- Okada YC, Salenius S (1998) Roles of attention, memory, and motor preparation in modulating human brain activity in a spatial working memory task. *Cereb Cortex* 8:80-96.
- Owen AM, Stern CE, Look RB, Tracey I, Rosen BR, Petrides M (1998) Functional organization of spatial and nonspatial working memory processing within the human lateral frontal cortex. *Proc Natl Acad Sci USA* 95:7721-7726.
- Papanicolaou AC, Simos PG, Breier JI, Zouridakis G, Willmore LJ, Wheeler JW, Constantinou JE, Gormley WB, Maggio WW (1999). Magnetoencephalographic mapping of the language-specific cortex. *J Neurosurg* 90:85-93.
- Passingham RE, Rowe JB (2002) Dorsal prefrontal cortex: maintenance in memory or attentional selection? In: Principles of frontal lobe function (Stuss DT, Knight RT, eds), pp. 221-232. New York: Oxford University Press.
- Passingham RE, Toni I, Rushworth MF (2000) Specialisation within the prefrontal cortex: the ventral prefrontal cortex and associative learning. *Exp Brain Res* 133:103-113.
- Paulesu E, Frith CD, Frackowiak RS (1993) The neural correlates of the verbal component of working memory. *Nature* 362:342-345.
- Petrides M (1995) Functional organization of the human frontal cortex for mnemonic processing. Evidence from neuroimaging studies. *Ann N Y Acad Sci* 769:85-96.
- Petrides M (2000a) The role of the mid-dorsolateral prefrontal cortex in working memory. *Exp Brain Res* 133:44-54.
- Petrides M (2000b) Mapping prefrontal cortical systems for the control of cognition. In: Brain mapping: the systems (Toga AW, Mazziotta JC, Frackowiak RS, eds), pp. 159-175. New York: Academic Press.
- Petrides M, Pandya DN (1999) Dorsolateral prefrontal cortex: comparative cytoarchitectonic analysis in the human and the macaque brain and corticocortical connection patterns. *Eur J Neurosci* 11:1011-1036.
- Petrides M, Alivisatos B, Meyer E, Evans AC (1993) Functional activation of the human frontal cortex during the performance of verbal working memory tasks. *Proc Natl Acad Sci USA* 90:878-882.
- Poldrack RA, Wagner AD, Prull MW, Desmond JE, Glover GH, Gabrieli JD (1999) Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. *Neuroimage* 10:15-35.
- Pollmann S, von Cramon DY (2000) Object working memory and visuospatial processing: functional neuroanatomy analyzed by event-related fMRI. *Exp Brain Res* 133:12-22.
- Postle BR, D'Esposito M (1999) 'What-then-where' in visual working memory: an event-related fMRI study. *J Cogn Neurosci* 11:585-597.
- Postle BR, Berger JS, Taich AM, D'Esposito M (2000) Activity in human frontal cortex associated with spatial working memory and saccadic behavior. *J Cogn Neurosci* 12(Suppl. 2):2-14.
- Prabhakaran V, Narayanan K, Zhao Z, Gabrieli JD (2000) Integration of diverse information in working memory within the frontal lobe. *Nat Neurosci* 3:85-90.
- Rama P, Sala JB, Gillen JS, Pekar JJ, Courtney SM (2001) Dissociation of the neural systems for working memory maintenance of verbal and nonspatial visual information. *Cogn Affect Behav Neurosci* 1:161-171.
- Rowe JB, Passingham RE (2001) Working memory for location and time: activity in prefrontal area 46 relates to selection rather than maintenance in memory. *Neuroimage* 14:77-86.
- Rowe JB, Toni I, Josephs O, Frackowiak RS, Passingham RE (2000) The prefrontal cortex: response selection or maintenance within working memory? *Science* 288:1656-1660.
- Rypma B, Prabhakaran V, Desmond JE, Glover GH, Gabrieli JD (1999) Load-dependent roles of frontal brain regions in the maintenance of working memory. *Neuroimage* 9:216-226.
- Sakai K, Rowe JB, Passingham RE (2002) Active maintenance in prefrontal area 46 creates distractor-resistant memory. *Nat Neurosci* 5:479-484.
- Sala JB, Rama P, Courtney SM (2003) Functional topography of a distributed neural system for spatial and nonspatial information maintenance in working memory. *Neuropsychologia* 41:341-356.
- Simos PG, Breier JI, Fletcher JM, Foorman BR, Castillo EM., Papanicolaou AC (2002) Brain mechanisms for reading words and pseudowords: an integrated approach. *Cereb Cortex* 12:297-305.
- Smith EE, Jonides J (1998) Neuroimaging analyses of human working memory. *Proc Natl Acad Sci USA* 95:12061-12068.
- Thomas KM, King SW, Franzen PL, Welsh TF, Berkowitz AL, Noll DC, Birmaher V, Casey BJ (1999) A developmental functional MRI study of spatial working memory. *Neuroimage* 10:327-338.
- Vallar G, Di Betta AM, Silveri MC (1997) The phonological short-term store-rehearsal system: patterns of impairment and neural correlates. *Neuropsychologia* 35:795-812.
- Veltman DJ, Rombouts SA, Dolan RJ (2003) Maintenance versus manipulation in verbal working memory revisited: an fMRI study. *Neuroimage* 18:247-256.
- Wiggs CL, Weisberg J, Martin A (1999) Neural correlates of semantic and episodic memory retrieval. *Neuropsychologia* 37:103-118.
- Zarahn E, Aguirre GK, D'Esposito M (1999) Temporal isolation of the neural correlates of spatial mnemonic processing with fMRI. *Brain Res Cogn Brain Res* 7:255-268.
- Zurowski B, Gostomzyk J, Gron G, Weller R, Schirrmeyer H, Neumeier B, Spitzer M, Reske SN, Walter H (2002) Dissociating a common working memory network from different neural substrates of phonological and spatial stimulus processing. *Neuroimage* 15:45-57.