WORKING MEMORY FOR ORDER AND THE PARIETAL CORTEX: AN EVENT-RELATED FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDY

C. MARSHUETZ,[a]* P. A. REUTER-LORENZ,[b1] E. E. SMITH,[c1] J. JONIDES[b1] AND D. C. NOLL[d1]

[a]*Department of Psychology, Yale University, 2 Hillhouse Avenue, New Haven, CT 06820-8205, USA*

[b]*Department of Psychology, The University of Michigan, 525 East University Avenue, Ann Arbor, MI 48109-1109, USA*

[c]*Department of Psychology, Columbia University, 1190 Amsterdam Avenue, New York, NY 10027, USA*

[d]*Department of Biomedical Engineering, Department of Radiology, The University of Michigan, 2200 Bonisteel Boulevard, Ann Arbor, MI 48109-2099, USA*

Abstract—Memory for order information has been tied to the frontal lobes, however, parietal activation is observed in many functional neuroimaging studies. Here we report functional magnetic resonance findings from an event-related experiment involving working memory for order. Five letters were presented for storage, followed after a delay by two probe items. Probe items could be separated by zero to three positions in the memory set and subjects had to indicate whether the items were in the correct order. Analyses indicate that activation in left parietal cortex shows a systematic decrease in activation with increasing probe distance. This finding is consistent with an earlier study in which we suggested that parietal cortical regions mediate the representation of order information via magnitude codes. © 2005 Published by Elsevier Ltd on behalf of IBRO.

Key words: distance effects, magnitudes, prefrontal cortex, temporal order, short-term memory, neuroimaging.

The question of how serial order is remembered is a classic issue in neuroscience and experimental psychology (Ebbinghaus, 1913; Lashley, 1951). Early research tied order memory to the frontal lobes by showing that frontal-lobe patients have difficulty making recency judgments (Milner, 1971). More recent work using single-cell recording in monkeys has confirmed prefrontal cortex (PFC) involvement by revealing cells in PFC that code for sequences (Averbeck et al., 2002; Carpenter et al., 1999).

Whereas many functional neuroimaging studies implicate the PFC in order memory (Cabeza et al., 1997; Henson et al., 2000; Konishi et al., 2002; Marshuetz et al., 2000; Suzuki et al., 2002; Zhang et al., 2002), there is

increasing evidence that the parietal cortex also plays a role. For instance, parietal activity has been reported in most neuroimaging studies of order memory (for a review, see Marshuetz, 2005). Despite this pervasive finding, reports have emphasized the role of the PFC, and consequently, the role of the parietal cortex in order memory has been largely unexplored.

What role does the parietal cortex play in coding or representing order? One way to approach the issue is to use the behavioral data to determine potential behavioral mechanisms, and combine that information with what is already known about other cognitive processes that are mediated by parietal cortex.

In a previous functional magnetic resonance imaging (fMRI) study of working memory for order information (Marshuetz et al., 2000), we observed several foci of activity in parietal cortex. In that experiment, each trial employed a memory set of five consonants. Order memory was tested with a probe that contained two items from the memory set, either in the correct order or transposed. Probe letters could be separated in the memory set by a distance of zero to three items (Fig. 1). For example, if participants held "D F G H J" in memory, they might be tested with a probe that was separated by a distance of a single item (e.g.,"F H") or by a distance of two items (e.g. "F J").

A number of different order-coding mechanisms have been proposed, and they make differential behavioral predictions for the task just described. For example, *inter-item association* ("chaining"), is a mechanism that forms links between items in the to-be-remembered series, for example, "D precedes F, F precedes G, G precedes H . . ." (e.g. Ebbinghaus, 1913; Kieras et al., 1999). A simple inter-item associative mechanism predicts that participants will respond more slowly and less accurately to probe items that are farther apart (e.g. "F J" in the previous example) than those closer together (e.g. "F H") because participants must traverse each link between the items to arrive at a decision.

A second potential mechanism is *direct coding*, in which each item in the set is tagged or categorized (Orlov et al., 2000) by its ordinal position ("D-first, F-second, G-third . . ."). Reaction times and errors will not differ based on the distance between the two probe items, because one simply needs to compare the tags or category labels to make a correct response.

In contrast to inter-item associations, *magnitude codes* (sometimes referred to as *temporal distinctiveness*, Neath and Crowder, 1990) make the opposite behavioral predic-
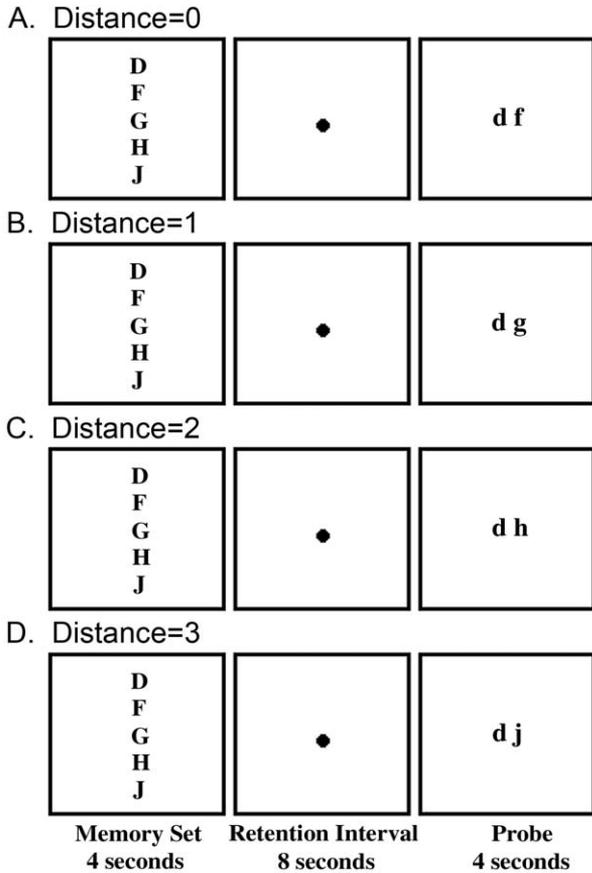
[1] E-mail addresses: parl@umich.edu (P. A. Reuter-Lorenz), eesmith@paradox.psych.columbia.edu (E. E. Smith), jjonides@umich.edu (J. Jonides), dnoll@umich.edu (D. C. Noll).
*Corresponding author. Tel: +1-203-432-4636; fax: +1-203-432-7172.
E-mail address: christy.marshuetz@yale.edu (C. Marshuetz).
Abbreviations: BA, Brodmann's area; DLPFC, dorsolateral prefrontal cortex; fMRI, functional magnetic resonance imaging; PFC, prefrontal cortex; ROI, region of interest.

Fig. 1. Example trials with different inter-item probe distances. When probe items were adjacent in the memory set, they had a distance of zero. A distance of three items is the case in which there were three intervening items in the memory set.

tion. According to this type of mechanism, order is coded in continuous, rather than discrete, form, much like an analog clock (Brown et al., 2000). Items that are closer together have codes that are more similar than those of items that are farther apart. Similarity should lead to longer reaction

times and more errors when the two items are in nearby temporal positions, a pattern of behavioral results commonly known as the *distance effect* (Moyer, 1973). This latter pattern is precisely what we observed in our study (Marshuetz et al., 2000): when the probe items had been close together in the memory set, participants responded more slowly and were more error-prone than when the items were drawn from more disparate positions.

Our next step was to identify other domains in which distance effects are observed and in which there is known parietal cortex involvement. One such domain is that of numerical representation and calculation (Chochon et al., 1999; Dehaene et al., 2003; Dehaene and Cohen, 1997; Pinel et al., 1999, 2001, 2004). Indeed, when we compared the order-related activations we observed with those in a study of numerical processing (Chochon et al., 1999), we found activation in the same parietal locations. Given the behavioral and neural similarities, we proposed that order information and numerical magnitudes may both be represented along a continuum of magnitude codes and that these codes are represented in parietal cortex (Marshuetz et al., 2000; Walsh, 2003).

Although we documented considerable parietal activation, a limitation of our previous study was that our blocked design prevented us from examining the activation data for systematic effects of probe distance, as has been done for numerical and other types of psychological distance (Pinel et al., 2001, 2004). Here we report data from an event-related fMRI experiment employing the same task (Fig. 2). Our goal was to determine whether the activation in parietal regions during the probe interval is affected by probe distance. A systematic relationship of activation with probe distance would lend credence to the idea that order is represented via magnitude codes or via a magnitude continuum.

EXPERIMENTAL PROCEDURES

Subjects

Twelve right-handed healthy subjects with no history of medical or psychiatric disease (six male; six female, age range 20–27 years,
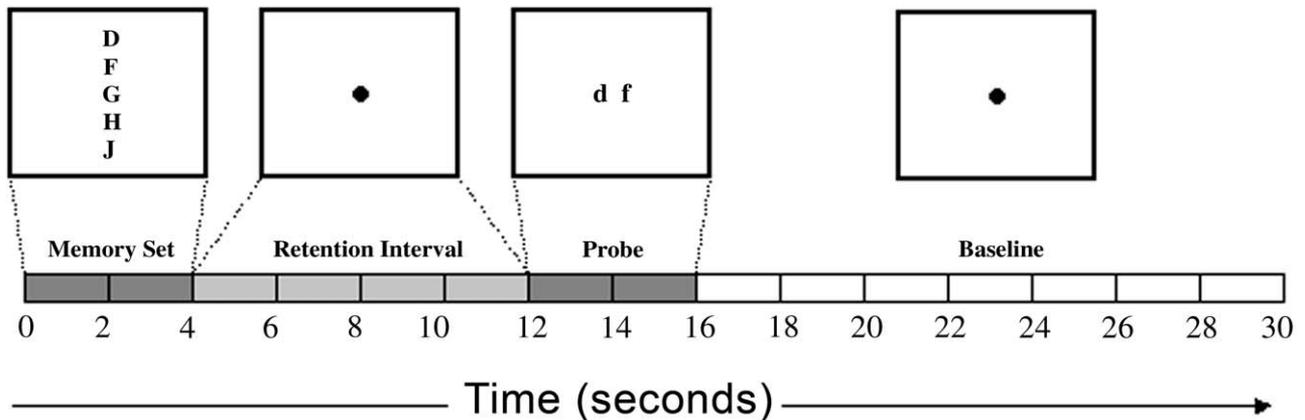

Fig. 2. Schematic representation of trial events. A full-brain volume was collected every two seconds (TR=2), indicated by boxes. Each trial began with presentation of the memory set for 4 s (2 TRs), after which participants were required to retain the items for 8 s. After the retention interval, a probe item appeared for four and participants made a yes/no decision via keypress. After the probe items disappeared, there was a resting baseline of 14 s.

mean age 22.5 years) gave written informed consent to participate in the study, which was approved by the institutional review board of the University of Michigan Medical School. Data from one subject were excluded because of excessive head movement (>5 mm).

Task

Stimuli were presented using PsyScope software (Cohen et al., 1993). Subjects saw five simultaneous upper-case consonants arrayed vertically, for 4 s. They were instructed to remember the items in order. After an 8-second delay, they responded to a probe (described below) which appeared for 4 s. The probe interval was followed by a resting baseline of 14 s (Fig. 2) during which a dot appeared in the center of the screen. Subjects were not required to maintain fixation. All consonants (with the exception of y) were used as stimuli were chosen randomly for each trial.

The probe consisted of two letters from the memory set, arrayed from left to right, either in the original order or transposed. Probe letters were presented in lower-case and varied randomly from a distance of 0–3 as in our previous experiment (Fig. 1). Responding to the question, "are these items in the correct order?" subjects depressed a key with the right index finger for positive responses and a second key with the right middle finger for negative responses. Subjects were required to respond while the probe items appeared on the screen; non-responses were counted as errors. Probe type was determined randomly with equal probability resulting in a roughly equal distribution of trial type for each participant.

Data acquisition and processing

Subjects completed nine fMRI runs [1.5 T GE LX scanner, spiral gradient echo sequence (Noll et al., 1995), TR=2000, TE=35, flip angle=80, FOV=20 cm]. There were a total of 63 30-second trials; seven trials per run. Slices were 4 mm thick, with an in-plane resolution of 3.125×3.125 acquired at 28 locations parallel to the anterior-posterior commissure line. The first seven volumes in each run were discarded to allow for T1 equilibration effects. All preprocessing was performed using Statistical Parametric Mapping software (SPM99, Wellcome Department of Cognitive Neurology, London) and consisted of: 1) correction for slice-acquisition timing to the middle slice, 2) realignment to the first volume in each run to correct for intra-scan movement, 3) normalization to a standard EPI template volume, 4) smoothing with a Gaussian kernel of 6 mm full-width at half maximum to accommodate anatomical variability across subjects.

Statistical analyses

All analyses were conducted on regions of interest (ROI) from our previous study (Marshuetz et al., 2000), which included three distinct areas of activity: left and right parietal cortex, and a superior frontal area (Brodmann's area (BA) 6). Since dorsolateral prefrontal cortex (DLPFC) activity was also of interest, we included an additional ROI in right DLPFC, found to be active in our previous study via ROI analysis. Analyses were conducted to answer two questions: The first was the question of how well the neural activity in this experiment replicated that of our earlier study. The second, more interesting, question was whether any of those areas showed evidence of distance effects.

A general linear model was applied to individual subject data to compute parameter estimates and *t*-statistic contrast maps for each voxel. Regressors were included for trials containing each probe type (distances of 0–3) as well as for errors, run, and signal drift. Trials with errors were eliminated from further analysis. Each trial was modeled as an epoch because of the event timing (>2 s). No derivatives were included. After model estimation, two contrasts were computed for each subject.

The first contrast compared activity during the Order task versus the 14-second resting baseline period. Individual subject images from this contrast were submitted to a random-effects group analysis in order to test the regions tied to the Order task in our previous study (Marshuetz et al., 2000) for significant activity.

We were particularly interested in the question of whether there would be a systematic effect of probe distance, as has been noted by Pinel and colleagues (1999, 2001) in their studies of numerical comparison. Therefore, the second analysis was a linear contrast testing for a negative slope relating activation to inter-item probe distance (using contrast weights −.75, −.25, 0.25, 0.75 to model distances of 0, 1, 2, and 3 respectively). As in the Order versus baseline analysis, images from this contrast were submitted to a random-effects group analysis. Because the parietal cortex is known to be involved in response preparation (Andersen and Buneo, 2002), we included an additional covariate in our *t*-test for the slope relating reaction time to distance for each participant in order to parcel out variance in activation due to reaction time differences across the conditions.

Four 12 mm spherical ROIs were defined, the peaks of which were the stereotaxic coordinates from our previous report. The first three were based on all significant regions of activation observed in our previous Order-Item contrast [left parietal cortex, −34, −46, 46; right parietal cortex, 26, −56, 52, right superior BA 6, 28, 2, 56]. The fourth region was in right DLPFC; 46, 39, 7, and was based on the only reliable prefrontal site to emerge from a ROI analysis in our earlier experiment (Marshuetz et al., 2000). We then examined activation in each ROI for significant main effects of Order-baseline and the relationship of activation to inter-item probe distance.

Finally, time-course data were extracted for the activation for each condition using an ROI toolbox (Russell Poldrack, http://spm-toolbox.sourceforge.net). Activation that occurred during the probe presentation and the four seconds immediately following probe offset (Fig. 2, scans corresponding to 12–20 s) were averaged for each type of trial and are graphically depicted in Fig. 3.

RESULTS

In the Order versus baseline contrast, significant activity was detected in both the left, *t*(10)=4.76, *P*<0.001, and right, *t*(10)=4.39, *P*=0.001, parietal cortex. Significant activity was also detected in the other two ROI, right superior BA 6, *t*(10)=2.50, *P*=0.016 and right DLPFC, *t*(10)=2.53, *P*=0.015. Thus, the areas shown to be active in the Order versus Item contrast and the prefrontal ROI analysis in our previous experiment were all active in the present experiment as well.

Activation in the left parietal cortex ROI, in or near the left intraparietal sulcus, had a significant linear relationship with probe distance, *t*(9)=2.87, *P*=0.009; without the reaction time covariate, *t*(10)=3.23, *P*=0.004. When we examined the activation data in the four time-points corresponding to the 8 s including and just after the probe presentation (scans corresponding 12–18 s in Fig. 2), it was the only region that showed strict monotonicity with probe distance (Fig. 3). Regions in the right parietal and right superior BA 6 also had significant linear relationships with distance, and *t*(9)=3.14, *P*=0.006, *t*(9)=3.39, *P*=0.004 respectively; without the reaction time covariate, *t*(10)=3.62, *P*=0.002 and *t*(10)=4.33, *P*=0.001. However, both deviated from strict monotonicity. Superior PFC showed evidence of a step function, with activation being greatest for probe items distances of 0 or 1 and smallest
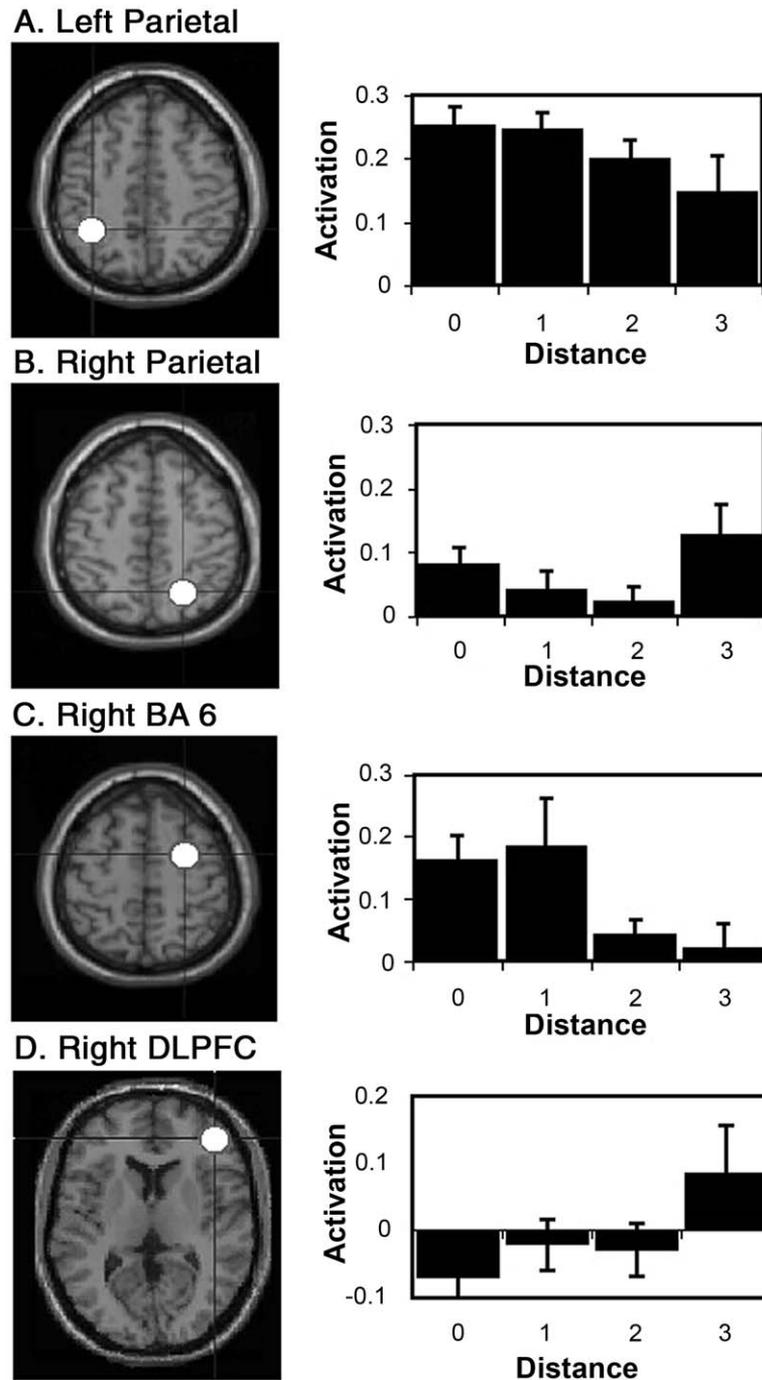
Fig. 3. Location of ROIs (left) and signal change in each (right). ROIs had a 12 mm radius and were centered on Talairach coordinates reported for Order-Item contrasts in Marshuetz et al. (2000). Panel (A) Left parietal cortex, coordinates=−34, −46, 46. Panel (B) Right parietal cortex, coordinates=26, −56, 52. Panel (C) Right superior BA 6, coordinates=28, 2, 56. Panel (D) Right DLPFC (BA 46), coordinates=46, 39, 7. The results of the distance analysis were not significant for this region. Note that the left parietal cortex shows a monotonic decrease in activation with increasing probe distance (Panel A), and that Superior 6 also shows hints of the effect (Panel C). Values approximate percent signal change from the first trial time-point.

for distances of 2 or 3. In right parietal cortex, activation is suggestive of a curvilinear relationship between activation and inter-probe distance (Fig. 3). Activation in the right DLPFC did not show a significant linear relationship with probe distance, $t(9)=1.74$, $P>0.05$; without reaction time as a covariate, $t(10)=1.79$, $P>0.05$. Behaviorally, the slope relating accuracy to distance was significant ($t=2.16$, $P=0.026$). Mean proportion correct (S.D.) for distances 0–3=.92 (0.04), 0.93 (0.04), 0.99 (0.04), 0.92, (0.09) respectively. There was no significant effect for reaction

time, because of the variability due to the small number of trials ($t=1.49$, $P>0.05$). Mean reaction times (S.D.) for distances $0–3=1798$ ms (383), 2058 ms (454), 2099 ms (559), 2008 ms (589) respectively.

DISCUSSION

The primary question under consideration was whether any of the regions we observed in an earlier study of order memory are related to distance representation. What we have found is that one region—in left parietal cortex— shows a systematic decrease in activation with increasing inter-item probe distance. This result is what would be expected if order is represented via a continuum, much the way numerical magnitudes appear to be coded and represented in parietal cortex (Pinel et al., 2001, 2004). There are also hints of distance effects in superior BA 6, although the activity does not appear to be as systematic as that observed in left parietal cortex. BA 6 is in close proximity to a region that has been shown to respond to distance in numerical comparison experiments (Pinel et al., 1999) and in at least one study of numerosity knowledge in monkeys (Neider et al., 2003). Future studies are needed to determine whether superior BA 6 responds to inter-item distance in order memory.

Although studies have suggested that the DLPFC is involved in memory for order, it does not appear to play a role in representing magnitude or distance in our task. It may be that the DLPFC is involved in tagging items with the appropriate order codes, whereas once items are coded for order, they are represented by the parietal cortex as a set of magnitudes. Alternatively, it may be the case that the DLPFC is involved in a more general supervisory role (Shallice, 1989), general task preparation (Sakai and Passingham, 2003), maintaining context information (Cohen and Servan-Schreiber, 1992) or a timing operation (Henson et al., 2000). Furthermore, it may be the case that there are different ways of coding and representing order depending on the task demands, and that they rely on different neural mechanisms.

One interesting question is why parietal activation decreases with increasing distance in our experiment and others (Pinel et al., 1999, 2001). There are at least two possible explanations. The first is that neurons in parietal cortex may become more excited as distance discriminations become more fine-grained. Alternatively, more activity may simply be the code for "close together" and less activation a code for "far apart." Either of these possibilities is consistent with our findings and those in other domains, like line orientation and numerical comparisons (Pinel et al., 1999, 2001; Fias et al., 2003). Further experimentation with neurophysiological techniques would help determine the specific underlying neural responses and suggest a more precise answer to this question.

Taken together with previous reports (Henson et al., 2000; Marshuetz et al., 2000; Suzuki et al., 2002; Konishi et al., 2002; Zhang et al., 2002), these results suggest the parietal cortex participates in a circuit of regions engaged in working memory for order. It is interesting to note that the parietal cortex has also been implicated in tasks of number processing and shows a significant relationship with numerical distance (Pinel et al., 1999, 2001, 2004). Such parietal effects also appear during judgments of the psychophysical distance between different line orientations (Fias et al., 2003), physical size, and luminosity (Pinel et al., 2004). The monotonic relationship we observed between left parietal cortex activation and inter-item distance is evidence that the parietal cortex has information about inter-item distances held in working memory.

REFERENCES

Andersen RA, Buneo CA (2002) Intentional maps in posterior parietal cortex. Annu Rev Neurosci 25:189–220.

Averbeck BB, Chafee MV, Crowe DA, Georgopoulos AP (2002) Parallel processing of serial movements in prefrontal cortex. Proc Natl Acad Sci U S A 99:13172–13177.

Brown GDA, Preece T, Hulme C (2000) Oscillator-based memory for serial order. Psychol Rev 107:127–181.

Cabeza R, Mangels J, Nyberg L, Habib R, Houle S, McIntosh AR, et al. (1997) Brain regions differentially involved in remembering what and when: A PET study. Neuron 19:864–870.

Carpenter AF, Georgopoulos AP, Pellizzer (1999) Motor cortical encoding of serial order in a context-recall task. Science 283:1752–1757.

Chochon F, Cohen L, van de Moortele PF, Dehaene S (1999) Differential contributions of the left and right inferior parietal lobules to number processing. J Cogn Neurosci 11:617–630.

Cohen JD, MacWhinney B, Flatt MR, Provost J (1993) PsyScope: A new graphic interactive environment for designing psychology experiments. Behav Res Methods Insturm Comput 25:257–271.

Cohen JD, Servan-Schreiber D (1992) Context, cortex and dopamine: A connectionist approach to behavior and biology in schizophrenia. Psychol Rev 99:45–77.

Dehaene S, Cohen L (1997) Cerebral pathways for calculation: Double dissociation between rote verbal and quantitative knowledge of arithmetic. Cortex 33:219–250.

Dehaene S, Piazza M, Pinel P, Cohen L (2003) Three parietal circuits for number processing. J Cogn Neuropsychol 20:487–506.

Ebbinghaus H (1913) Memory: A contribution to experimental psychology. New York: Columbia University, Teachers College.

Fias W, Lammertyn J, Reynvoet B, Dupont P, Orban GA (2003) Parietal representation of symbolic and nonsymbolic magnitude. J Cogn Neurosci 15:47–56.

Henson RNA, Burgess N, Frith CD (2000) Recoding, storage, rehearsal and grouping in verbal short-term memory: an fMRI study. Neuropsychologia 38:426–440.

Kieras DE, Meyer DE, Mueller S, Seymour T (1999) Insights into working memory from the perspective of the EPIC architecture for modeling skilled perceptual-motor and cognitive human performance. In: Models of working memory: mechanisms of active maintenance and executive control (Miyake AL, Shaw P, eds), pp 183–223. Cambridge, UK: Cambridge University Press.

Konishi S, Uchida I, Okuaki T, Machida T, Shiruzu I, Miyashita Y (2002) Neural correlates of recency judgment. J Neurosci 22:9549–9555.

Lashley KS (1951) The problem of serial order in behavior. In: Cerebral mechanisms in behavior (Jeffress LA, ed), pp 112–136. New York: Wiley.

Neider A, Freedman DJ, Miller EK (2003) Representation of the quantity of visual items in the primate prefrontal cortex. Science 297:1708–1711.

Marshuetz C (2005) Order information in working memory: An integrative review of evidence from brain and behavior. Psychol Bull 131:323–339.

Marshuetz C, Smith EE, Jonides J, DeGutis J, Chenevert TL (2000) Order information in working memory: fMRI evidence for parietal and prefrontal mechanisms. J Cogn Neurosci 12 (Suppl 2):130–144.

Milner B (1971) Interhemispheric differences in the localization of psychological processes in man. Br Med Bull 27:272–277.

Moyer RS (1973) Comparing objects in memory: evidence suggesting an internal psychophysics. Percept Psychop 13:180–184.

Neath I, Crowder RG (1990) Schedules of presentation and temporal distinctiveness in human memory. J Exp Psychol Learn Mem Cogn 16:316–327.

Noll DC, Cohen JD, Meyer CH, Schneider W (1995) Spiral k-space MRI of cortical activation. J Magn Reson Imaging 5:49–56.

Orlov T, Yakovlev V, Hochstein S, Zohary E (2000) Macaque monkeys categorize images by their ordinal number. Nature 404:77–80.

Pinel P, Le Clec'H G, van de Moortele PF, Naccache L, Le Bihan D, Dehaene S (1999) Event-related fMRI analysis of the cerebral circuit for number comparison. NeuroReport 10:1473–1479.

Pinel P, Dehaene S, Riviere D, Le Bihan D (2001) Modulation of parietal activation by semantic distance in a number comparison task. Neuroimage 14:1013–1026.

Pinel P, Piazza M, Le Bihan D, Dehaene S (2004) Distributed and overlapping cerebral representations of number, size, and luminance during comparative judgments. Neuron 41:983–993.

Sakai K, Passingham RE (2003) Prefrontal interactions reflect future task operations. Nat Neurosci 6:75–81.

Shallice T (1989) From neuropsychology to mental structure. Cambridge, UK: Cambridge UP.

Suzuki M, Fujii T, Tsukiura T, Okuda J, Umetsu A, Nagasaka T, et al (2002) Neural basis of temporal context memory: A functional MRI study. Neuroimage 17:1790–1796.

Walsh V (2003) A theory of magnitude: common cortical metrics of time, space, and quantity. Trends Cogn Sci 7:481–483.

Zhang DR, Li ZH, Chen XC, Wang ZX, Zhang XC, Xiao MM, et al. (2002) Functional comparison of primacy, middle, and recency retrieval in human auditory short-term memory: an event-related fMRI study. Cogn Brain Res 16:91–98.