Pergamon

PII: S0028-3932(97)00072-9

Neuropsychologia, Vol. 35, No. 10, pp. 1373–1380, 1997

Printed in Great Britain
0028-3932/97 $17.00+0.00

Dissociating working memory from task difficulty in human prefrontal cortex

DEANNA M. BARCH,¶* TODD S. BRAVER,† LEIGH E. NYSTROM,*
STEVEN D. FORMAN,‡ DOUGLAS C. NOLL§ and JONATHAN D. COHEN*†

*Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA 15213, U.S.A.; †Department of Psychology, Carnegie Mellon, Pittsburgh, PA 15213, U.S.A.; ‡Department of Psychiatry, Highland Drive Department of Veterans Affairs Medical Center and Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA 15206, U.S.A.; §Department of Radiology, University of Pittsburgh, Pittsburgh, PA 15213, U.S.A.

(*Received* 26 *October* 1996; *accepted* 22 *April* 1997)

Abstract—A functional magnetic resonance imaging (fMRI) study was conducted to determine whether prefrontal cortex (PFC) increases activity in working memory (WM) tasks as a specific result of the demands placed on WM, or to other processes affected by the greater difficulty of such tasks. Increased activity in dorsolateral PFC (DLPFC) was observed during task conditions that placed demands on active maintenance (long retention interval) relative to control conditions matched for difficulty. Furthermore, the activity was sustained over the entire retention interval and did not increase when task difficulty was manipulated independently of WM requirements. This contrasted with the transient increases in activity observed in the anterior cingulate, and other regions of frontal cortex, in response to increased task difficulty but not WM demands. Thus, this study established a double-dissociation between regions responsive to WM versus task difficulty, indicating a specific involvement of DLPFC and related structures in WM function. © 1997 Elsevier Science Ltd

Key Words: neuroimaging; Continuous Performance Test; Broca's area; parietal cortex; anterior cingulate; task difficulty.

Introduction

Numerous functional neuroimaging studies have demonstrated activation of dorsolateral prefrontal cortex (DLPFC) during task conditions that engage working memory (WM) [9, 13, 23, 25, 28, 33]. Furthermore, such activation correlates positively with WM load [4]. These findings provide the strongest evidence available to date from human studies that DLPFC plays a role in WM function. However, in all of these studies, the conditions used to engage WM have been confounded with increased task difficulty and poorer performance on the part of participants. This raises an important concern that the previous findings may be explained by processes other than WM that are affected by increases in task difficulty. A common form of this argument is that the more difficult WM conditions are more effortful to perform, and that the DLPFC activation may merely reflect this increase in 'mental effort' or arousal, rather than a specific role in WM function. This is a fundamental and limiting issue in research concerning DLPFC, that must be resolved in order for research to progress on the information processing function(s) subserved by this brain region. Unfortunately, it is difficult to directly address questions regarding mental effort and arousal, in part because these concepts are often used too generally to be properly operationalized. However, it is possible that there are specific processes (e.g. resource allocation, error monitoring) that are engaged by manipulations that increases task difficulty, even if the manipulation has no effect on WM demand. As such, these processes may be dissociable from ones directly related to WM function.

The current study, using functional magnetic resonance imaging (fMRI), was designed to find such a dissociation, and to establish whether WM demand or task difficulty is responsible for activation of DLPFC. Our design involved two experimental manipulations. The first probed WM function and allowed us to determine whether activity in DLPFC increases as a function

¶ Authorship order of the first two authors was arbitrary, and was decided by a coin flip. Correspondence concerning this manuscript should be addressed to either of the first two authors at the Department of Psychology, Carnegie Mellon University, Pittsburgh, PA 15213, U.S.A.; e-mail: dba9@andrew.cmu.edu or tb2j@andrew.cmu.edu; fax: 412-624-3429.

of greater WM demand, even when task difficulty does not increase. The second manipulation increased task difficulty independently of WM, allowing us to address the question of whether activity in DLPFC increases as a function of increased task difficulty, even when WM demands do not change. We operationalized task difficulty in terms of behavioral performance. Thus, an experimental manipulation that produces a decrement in performance was assumed to increase task difficulty, whereas a manipulation that does not produce such a decrement was assumed not to affect task difficulty. Using this design, we sought to identify regions that showed a double-dissociation between responsivity to WM demands versus task difficulty, and thereby convincingly establish the specificity of their respective functions.

To probe WM function, we used a task that we have studied extensively in behavioral and computational modeling work. The task was a variant of the Continuous Performance Test (CPT [30]), which required subjects to monitor a sequence of visually presented single letters, for the presence of a pre-specified probe (e.g. X), and respond to it whenever it follows a particular cue (e.g. A). Thus, correct responding required memory of the prior stimulus. We manipulated memory demand by varying the delay between the cue and probe stimuli. We chose this task for the following reasons. First, we assumed that a long delay (8 sec) would require subjects to actively maintain cue information in WM over the interval, while a short delay (1 sec) would significantly reduce such demands. In computational modeling studies of this task, we have made this assumption explicit [5, 8, 12]. Second, in this work, we have additionally postulated that the cue information is maintained in DLPFC [5, 8, 12]. Third, in behavioral studies, we have interpreted the delay-related impairments observed in schizophrenia patients on this task as due to a specific deficit in WM function, and have suggested that this deficit is related to a disturbance in DLPFC [7, 12, 32]. However, in controls, we have found that behavioral performance is not affected by increased delay [32]. Thus, in the current study, we predicted that task difficulty would be equated across the long and short delay conditions of the AX–CPT, but that DLPFC would show increased activity at the long delay relative to the short.

To examine the effects of task difficulty independently of WM function, we included a manipulation of stimulus degradation. In previous studies, we have shown that visually degrading stimuli significantly decreases performance in this task, equally in the long and short delay conditions [3]. Thus, this manipulation increases task difficulty by changing perceptual requirements, but it does not interact with memory demands. Consequently, we predicted that regions of prefrontal cortex (PFC) that increased activity in response to the delay manipulation would not increase activity in response to the degradation manipulation. Confirmation of this prediction, together with the demonstration of activation elsewhere in response to the degradation manipulation, would satisfy our goal of demonstrating a double-dissociation between areas responsive to the demands of WM versus task difficulty.

Methods

Subjects

Informed consent was obtained from eleven neurologically normal righthanded subjects. Subjects were seven males and four females, with a mean age of 32 (range 25 to 42 years). All subjects were given a pretesting session, in which they practiced the task, and were included only after reaching an acceptable level of performance (> 75% accuracy on all conditions).

Cognitive tasks

Subjects performed our version of the AX–CPT [3, 7, 32]. In this task, subjects observed sequences of letters presented one at a time, and responded to an X but only when it followed an A. To influence WM demand, we varied the delay between the cue (A/non-A) and the probe (X/non-X). A factorial design was used, with two levels of memory (short versus long delay) fully crossed with two levels of task-difficulty (non-degraded versus degraded), yielding four task conditions. Trials were blocked by condition, and an equal number of blocks were run in each of the four conditions.

Subjects observed stimuli (single capital letter in 24 point Helvetica font) presented centrally on a visual display, and responded using a hand-held response box with fiber-optic connections to a Macintosh computer in the scanner control room running PsyScope software [10]. Trials in all conditions lasted 10 sec (see Fig. 1), and included a cue, a delay period (retention interval), a probe, and an intertrial interval (ITI). Cue and probe durations were 0.5 sec. In long delay trials, the retention interval was 8 sec and the ITI was 1 sec. In short delay trials this was reversed, to control for general factors (e.g. pace of the task, total task duration, etc.), and thereby help equate behavioral performance. In the non-degraded conditions stimuli appeared intact, while in degraded conditions 85% percent

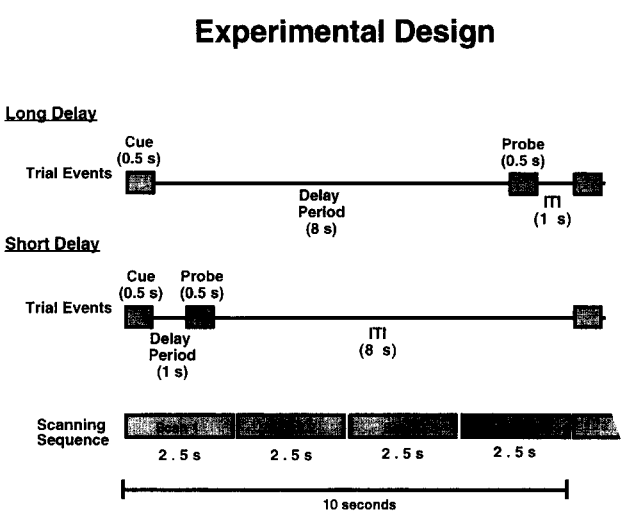

Fig. 1. Schematic of the experimental design, showing a timeline of the events occurring in each trial in the short and long delay blocks, and the timing of scan acquisition.

of the pixels were randomly removed from each stimulus. Subjects responded to every stimulus (cue and probe) with their dominant hand, pressing one button for target events (X appearing consecutively after an A) and an adjacent button for non-target events. Target sequences (A–X) occurred on 70% of trials. The remaining 30% of trials were divided equally among three types of non-target sequences: 1) invalid cue–target probe (e.g. B–X); 2) valid cue–non-target probe (e.g. A–Y); and 3) invalid cue–non-target probe (e.g. B–Y). In previous studies, we have found this distribution of target and non-target sequence frequencies to be useful for examining the effects of WM function on behavioral performance [3, 7, 32]. Subjects were scanned while performing the task continuously for 2-min blocks, each of which contained 12 trials. There was a brief delay (approximately 10–20 sec) between blocks, allowing the subject to rest, and the hemodynamic response to recover prior to the next block. Six blocks of each of the four conditions were run in a pseudorandom order, such that all conditions were sampled once in every set of four blocks.

MRI scanning procedures

Images were acquired with a 1.5T GE Signa whole body scanner. Twenty-four slices (3.75 mm^3 isotropic voxels) were acquired parallel to the AC–PC line. Functional scans were acquired with a 4-interleave spiral–scan pulse sequence (TR = 640 msec, TE = 35 msec, FOV = 24 cm, flip = 40°) [26]. This pulse sequence allowed 8 slices to be acquired every 2.5 s. Scanning was synchronized with stimulus presentation so that 4 scans of 8 slice locations were acquired during each 10 s trial (see Fig. 1). A first set of 8 locations was scanned for three consecutive trials, followed by two additional sets of 8 different locations, each scanned during three consecutive trials. The order in which slice locations were acquired was counterbalanced within subjects across blocks, as well as across subjects. Scanning occurred during only 9 of the 12 trials in each block, with the remainder used to allow the MRI signal to achieve steady state. A total of 18 scans per time point per slice location per task condition were acquired. This is the same rapid scanning technique that we have used in another recently completed study [11], which allowed us to track the temporal dynamics of activation within each trial. Anatomical scans were acquired at the same locations as the functional images, using a standard T1-weighted pulse sequence.

Image analysis procedures

Images were co-registered and pooled across subjects using a procedure similar to one used in PET studies [38]. We have used this procedure in previous fMRI studies to increase statistical power and permit direct quantitative identification of regions that change activity reliably across subjects [4, 11]. Participants' structural images were aligned to a reference brain using an automated algorithm [37]. All functional images were corrected for movement (using a 3-D version of the same algorithm) and scaled to a common mean (to reduce the effect of scanner drift or instability). The functional images were then registered to the reference brain using the alignment parameters derived for the structural scans, and smoothed using an 8 mm FWHM Gausslan filter (to reduce the effects of anatomic variability across subjects). The imaging data, pooled across subjects, were then analyzed using a voxelwise 3-way ANOVA, with delay (short versus long), difficulty (non-degraded versus degraded), and scan within trial [14] as factors. Statistical maps of the voxelwise *F*-ratios for each main effect and the interaction terms were generated, and then thresholded for significance using a clustersize algorithm [17]. This algorithm takes account of the spatial extent of activation to correct for multiple comparisons. A cluster-size threshold of 8 voxels and a per-pixel alpha of 0.005 was chosen, corresponding to an image-wise false positive rate of 0.005. Areas of significant activation were subjected to planned contrasts, to confirm that significant effects conformed to predicted patterns. Finally, the anatomical location of each active region was determined by reference to the Talairach atlas [34].

Behavioral data analysis procedures

Performance was assessed using measures of signal-discrimination (d′) [22] and reaction time (RT). D′ was computed for each subject in each task condition using the hit rate and false alarm rates for target and distractor trials respectively. Mean RT was computed for each subject in each condition using only correct responses. These data were then analyzed using a 2-way ANOVA with delay and degradation as factors.

Results

Behavioral data

First, we examined the behavioral data. The results of the d′ ANOVA indicated a significant main effect of degradation [non-degraded: M = 4.33, S.E. = 0.08; degraded: M = 3.58; S.E. = 0.12; $F(1,10) = 35.10$, $P < .001$], but no main effect of delay [short: M = 4.06; S.E. = 0.13; long: M = 3.85, S.E. = 0.12; $P > 0.20$] and no delay X degradation interaction ($P > 0.14$). The results of the RT ANOVA were identical: a significant main effect of degradation [non-degraded: M = 592, S.E. = 19.0; degraded: M = 679; S.E. = 23.4; $F(1,10) = 56.93$, $P < 0.001$], but no main effect of delay [short: M = 627; S.E. = 22.7; long: M = 645, S.E. = 23.7; $P > 0.10$] and no delay X degradation interaction ($P > 0.80$). Thus, behavioral performance was comparable at the short and long delay conditions, measured both by accuracy and reaction time. This result confirms that task difficulty was successfully equated across the short and delay conditions, dissociating our WM manipulation from an increase in task difficulty. Further, as predicted, behavioral performance was significantly worse in the degraded conditions, as measured both by accuracy and reaction time, and there was no interaction of degradation with delay. This result corroborates our previous findings using this task [3], and confirms that our degradation manipulation successfully increased task difficulty independent of the WM demands of this task.

Imaging data

Effect of delay.. Next, we examined the effect of the WM manipulation (i.e. delay) on brain activation. Three brain regions showed a significant main effect of delay, with greater activation in the long relative to the short

delay condition: left middle frontal gyrus (see Fig. 2a), left inferior frontal gyrus, and left posterior parietal lobule. As shown in Table 1, the middle frontal gyrus region corresponded to DLPFC, and the left inferior frontal gyrus region corresponded to Broca's area. Furthermore, analysis of the effect of time (scan-within-trial) showed no interactions of delay and time in either DLPFC or Broca's area. Thus, activity was increased in the long delay condition similarly across all four scans of the trial in these regions (see Fig. 2b). However, the region within parietal cortex did exhibit a delay X scan-within-trial interaction ($p < .05$), such that the difference between activity in the short and long delay conditions varied across scans.

Effect of task difficulty.. We next examined the effects of the task difficulty manipulation on brain activation. There were no main effects of task difficulty in any of the regions that changed activity in response to the WM demands of the task. Further, the only delay X task difficulty interaction that approached significance in these regions was in left DLPFC ($P = 0.05$). However, as shown in Fig. 2c, this interaction was in the direction opposite to that predicted by the hypothesis that DLPFC activity reflects task difficulty demands rather than WM demands. That is, activity was overall lower in the more difficult degraded condition, and there was no increase in delay-related DLPFC activation under degradation. One might still argue that the absence of significant task difficulty effects reflect insufficient power in the experiment. However, several other regions showed difficulty-related increases in activity, including anterior cingulate, right inferior frontal cortex, and a subcortical region (see Fig. 3a and Table 1). These difficulty effects were observed as a task difficulty X time (scan within trial) interaction, rather than as a main effect of task difficulty. The largest and most strongly affected of these regions was the anterior cingulate (see Table 1). As shown in Fig. 3(b), the time course data shows that activity peaked in the middle two scans, and then decayed. This pattern is consistent with transient neural activity occuring at the beginning of the trial convolved with the well-characterized 3–5-sec lag in the hemodynamic response (which is what the fMRI signal measures, e.g. [24]). The interaction in anterior cingulate (and in the other regions as well) arose from increased activity in the degraded

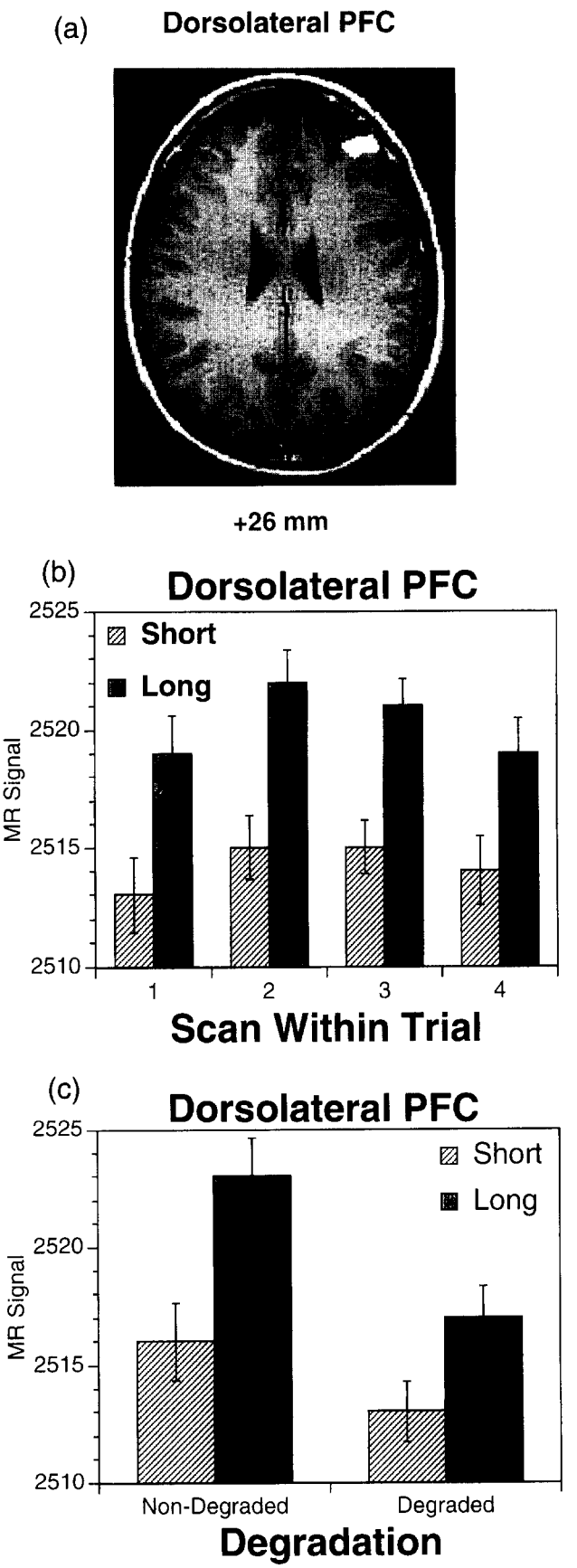

Fig. 2. (a) An image encompassing the region within DLPFC that exhibited a significant delay-related increase in activity. The image is displayed in radiological convention, with the right side of the image corresponding to the subject's left. The region was identified as described in the text, and is shown in an axial slice overlaid on corresponding anatomical reference image. (b) Activity in short and long delay conditions plotted separately for each the four scans within a trial for the DLPFC region. (c) Activity in short and long delay conditions plotted separately for the nondegraded and degraded conditions for the DLPFC region. A similar pattern was also found in the left inferior frontal cortex region.

Table 1. Significant activation as a function of delay and task difficulty

Regions of interest	Brodmann area(s)	X*	Y*	Z*	Volume (mm^3)†	Maximum *Z*-score‡
Main effect of delay						
Left DLPFC	46/9	−37	42	29	1139	3.25
Left inferior frontal cortex	44/6	−57	2	13	1594	3.36
Left parietal cortex	40/7	−40	−50	50	555	3.05
Interaction of task difficulty and scan-within-trial						
Anterior cingulate	8/32	4	25	43	2530	4.16
Right inferior frontal cortex	44/45	48	19	23	1478	4.04
Right inferior frontal cortex	45/47	50	19	2	690	3.76
Basal ganglia	-	25	−1	9	1338	3.40

*X, Y, and Z are coordinates in a standard stereotactic space [34] in which positive values refer to regions right of (X), anterior to (Y), and superior to (Z) the anterior commissure (AC).

†Volume refers to the number of voxels (converted to mm^3) which reached statistical significance in each region of interest.

‡*F* values were converted to *Z*-scores to provide a measure of effect size independent of sample size.

conditions that primarily affected the later scans of the trial.

Discussion

The results of this study establish a double-dissociation between regions responsive to WM demands versus those responsive to task difficulty. Specifically, DLPFC, left inferior frontal cortex (Broca's area), and a region in left parietal cortex showed significantly greater activity in the long compared to short delay conditions of the task, but did not show greater activity as a function of the task difficulty manipulation. In contrast, several other regions, including anterior cingulate, showed greater activity in the more difficult task conditions, but did not demonstrate greater activity as a function of the delay manipulation. Thus, our findings strongly support the hypothesis that regions within frontal cortex (including DLPFC and Broca's area) as well as parietal cortex are specifically engaged by WM demands, rather than by other processes that may be affected by increases in task difficulty. These findings address the confound between task difficulty and WM demands, which has represented a fundamental methodological and conceptual problem with previous studies implicating DLPFC (and associated areas) in WM.

The three cortical regions affected by the delay manipulation—DLPFC, Broca's area, and parietal cortex—consistently co-activate in WM tasks, and have been thought to comprise a neural circuit underlying verbal WM [1, 4, 28]. As such, our findings strongly support the hypothesis that the delay manipulation engages WM. Further, the subtle nature of the task manipulation, the equating of task difficulty across the short and long delay conditions, and the discrete, circumscribed nature of identified regions, suggest that this task may be particularly suited to probing both WM and PFC function. In addition, the fact that DLPFC and Broca's area showed greater activation in the long relative to short delay conditions is consistent with our hypotheses that: (1) the maintenance of the cue information over a long delay involves DLPFC [5, 8, 12]; and (2) schizophrenic behavioral impairments in this version of the CPT may be related to DLPFC dysfunction [7, 12, 32]. However, parietal cortex also increased activity as a function of delay. Thus, although our findings strongly support the hypothesis that DLPFC, Broca's area, and parietal cortex are specifically engaged by WM demands, the exact functional contribution of each of these areas has not yet been identified.

WM involves a number of different processes, including active maintenance as well as more transient functions, such as the updating of WM contents and comparison operations [2]. In the current study, we found that DLPFC and Broca's area displayed a pattern of sustained activation throughout the delay period between cue and probe. In Cohen *et al.* [11], DLPFC and Broca's area also displayed sustained activation throughout the retention interval of a sequential letter memory task ('n-back'). Together, these results support the view that regions within DLPFC and Broca's area are specifically involved in active maintenance. Activation in the n-back task appeared in a different region of DLPFC than found in the present study, which may reflect a difference in the type of information to be maintained. Specifically, the letter memory task requires maintenance of sequential order information, while the AX–CPT does not. Such dissociations are consistent with neurophysiological findings from non-human primates suggesting the involvement of DLPFC in active maintenance [18, 19, 21], with different areas responsible for maintaining different types of information [36]. Interestingly, the effect of delay on activity in parietal cortex was different from that found in DLPFC and Broca's area. Specifically, the delay-effect in parietal cortex interacted with scan-within-trial, whereas no such interactions were found in the two PFC regions. This suggests the possibility that this region of parietal cortex may be involved in other WM-related processes in addition to (or instead of) active maintenance.

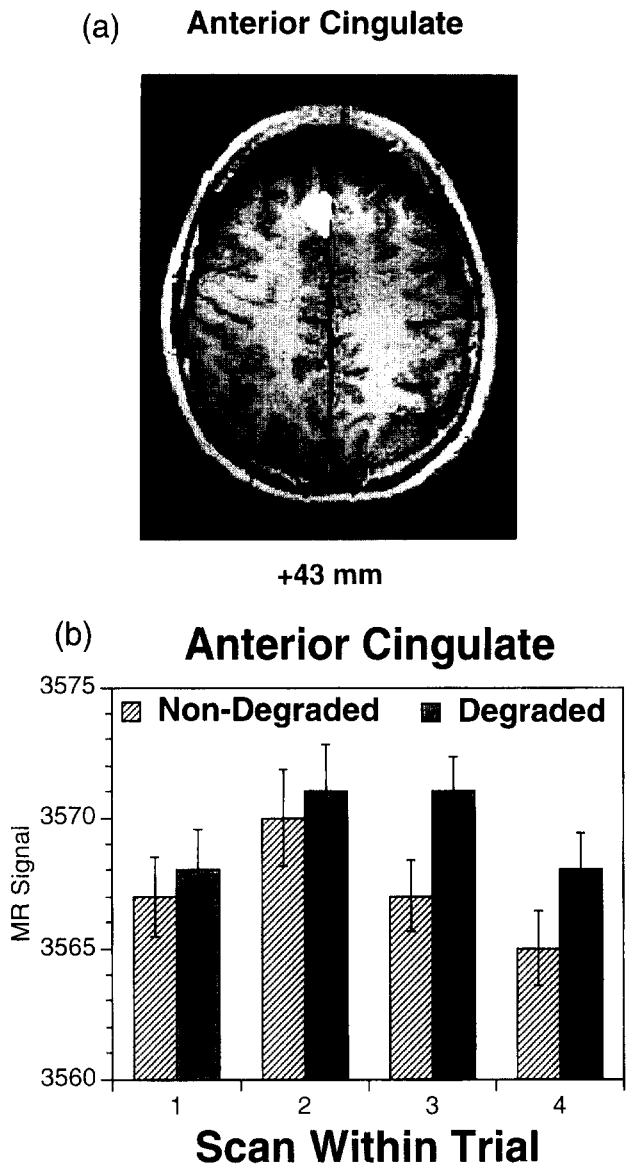

Fig. 3. (a) An image encompassing the region within anterior cingulate that exhibited significant activation in response to increased task difficulty. (b) Activity in nondegraded and degraded conditions plotted separately for each the four scans within a trial for the anterior cingulate region. A similar pattern was also found in the other regions showing, an effect of task difficulty.

In the present study, the effects of task difficulty were observed as interactions between degradation and time-within-trial, rather than as a main effect of degradation. The time course data suggest that changes in activity due to degradation were of a transient rather than a sustained nature. Our interpretation of this pattern is that the degradation manipulation primarily affected processess engaged during stimulus processing and response, and not during active maintenance. Under this interpretation, there are two possible explanations for the specific pattern observed. The first is that under degradation, these processes took longer and thus the peak of activity in the degraded conditions occurred later than the peak of activity in the non-degraded conditions (see Fig. 3b). Another possibility is that under degradation, the processes were of greater intensity, but equal duration. This situation could result in the observed pattern of data through the convolution of neural activity with a non-linear hemodynamic response function [31, 35]. In other words, processes that are of greater intensity may take longer to return to baseline.

It is interesting that the area most strongly affected by the task difficulty manipulation was the anterior cingulate. While the function of this brain structure is still poorly understood, it has frequently been observed in WM and related tasks [6, 9, 27, 29, 33], as well as studies that have explicitly manipulated task difficulty [14]. In the present study, the anterior cingulate did not increase activity in response to the WM manipulation. However, our manipulation of WM demand (i.e. delay interval) did not alter task difficulty. As such, our findings are consistent with the possibility that the anterior cingulate may be involved in the mediation of motivational and/or affective responses to task difficulty. This would be consistent with the close relationship of this structure to the limbic structures of the brain [16]. Alternatively, or in addition, it is possible that the anterior cingulate plays a role in more cognitive functions, such as resource allocation or error detection and compensation [15, 20]. Of course, additional studies will be required to evaluate these possibilities, and to further characterize the relationship of the anterior cingulate to other structures involved in WM function.

Acknowledgements—This work was supported in part by grants from the McDonnell Foundation (JDC) and the National Institute of Mental Health (JDC). The authors thank Charles Hachten, Cheryl Gach, and Fred Sabb for their technical assistance, and Marlene Behrmann, Cameron Carter, and Walter Schneider for their thoughtful comments and helpful suggestions.

References

1. Awh, E., Jonides, J., Smith, E. E., Schurnacher, E. H., Koeppe, R. and Katz, S. Dissociation of storage and rehearsal in verbal working memory: Evidence from PET. *Psychological Science* **7**, 25–31, 1996.
2. Baddeley, A. D., *Working Memory*. Oxford University Press, New York, 1986.
3. Braver, T. S., Barch, D. M. and Cohen, J. D., Inducing schizophrenic-like performance in controls: Validation for a theon, of working memory, deficits in schizophrenia. Paper presented at the Society for Research in Psychopathology, 11th Meeting, Atlanta, GA, 1996.
4. Braver, T. S., Cohen, J. D., Nystrom, L. E., Jonides, J., Smith, E. E., Noll, D. C. A parametric study of prefrontal cortex involvement in human working memory. *NeuroImage* **5**, 49–62, 1997.
5. Braver, T. S., Cohen, J. D. and Servan-Schreiber, D., A computational model of prefrontal cortex function. In *Advances in Neural Information Processing*

Systems, ed. D. S. Touretzky, G. Tesauro and T. K. Leen, Vol. 7. MIT Press, Cambridge, MA, 1995, pp. 141–148.
6. Carter, C. S., Mintun, M., Cohen, J. D. Interference and facilitation effects during selective attention: An [^{15}O]–H_2O PET study of Stroop task performance. *NeuroImage* **2,** 264–272, 1995.
7. Cohen, J. D., Barch, D. M., Carter, C. S., Servan-Schreiber, D. Schizophrenic deficits in the processing of context: Converging evidence from three theoretically motivated cognitive tasks. *Biological Psychiatry* **39,** 608–609, 1996.
8. Cohen, J. D., Braver, T. S. and O'Reilly, R. A computational approach to prefrontal cortex, cognitive control, and schizophrenia: Recent developments and current challenges. *Philosophical Transactions of the Royal Society Series B* **346,** 1515–1527, 1996.
9. Cohen, J. D., Forman, S. D., Braver, T. S., Casey, B. J., Servan-Schreiber, D., Noll, D. C. Activation of prefrontal cortex in a nonspatial working memory task with functional MRI. *Human Brain Mapping* **1,** 293–304, 1994.
10. Cohen, J. D., MacWhinney, B., Flatt, M. R. and Provost, J. PsyScope: A new graphic interactive environment for designing psychology experiments. *Behavioral Research Methods, Instruments & Computers* **25,** 257–271, 1993.
11. Cohen, J. D., Perlstein, W. M., Braver, T. S., Nystrom, L., Noll, D. C., Jonides, J. and Smith, E. E., Temporal dynamics of brain activation during a working memory task. *Nature* **386,** 604–608, 1997.
12. Cohen, J. D., Servan-Schreffier, D. Context, cortex and dopamine: A connectionist approach to behavior and biology in schizophrenia. *Psychological Review* **99,** 45–77, 1992.
13. Courtney, S. M., Ungerleider, L. J., Keil, K., Haxby, J. V. Object and spatial visual working memory activate seperate neural systems in human cortex. *Cerebral Cortex* **6,** 3949, 1996.
14. D'Esposito, M., Detre, J. A., Alsop, D. C., Shin, R. K., Atlas, S. and Grossman, M. The neural basis of the central executive system of working memory. *Nature* **378,** 279–281, 1995.
15. Dehaene, S., Posner, M. I., Tucker, D. M. Localization of a neural system for error detection and compensation. *Psychological Science* **5,** 303–306, 1994.
16. Devinsky, O., Morrell, M. J. and Vogt, B. Contributions of anterior cingulate cortex to behavior. *Brain* **119,** 279–306, 1995.
17. Forman, S. D., Cohen, J. D., Fitzgerald, M., Eddy, W. F., Mintun, M. A., Noll, D. C. Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): Use of a cluster-size threshold. *Magnetic Resonance in Medicine* **33,** 636–647, 1995.
18. Funahashi, S., Bruce, C. J., Goldman-Rakic, P. S. Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. *Journal of Neurophysiology* **61,** 331–349, 1989.
19. Fuster, J. M., *The Prefrontal Cortex: Anatomy, Physiology and Neuropsychology of the Frontal Lobe.* Raven Press, New York, 1989.
20. Gehring, W. J., Goss, B., Coles, M. G.H., Meyer, D. E. and Donchin, E. A neural system for error detection and compensation. *Psychological Science* **4,** 385–390, 1993.
21. Goldman-Rakic, P. S., Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In *Handbook of Physiology—The Nervous System*, ed. F. Plum and V. Mountcastle, Vol. 5. American Physiological Society, Bethesda, MD, 1987, pp. 373–417.
22. Green, D. M. and Swets, J. A., *Signal Detection Theory and Psychophysics.* Robert E. Krieger Publishing Co., Huntington, N.Y., 1966.
23. Jonides, J., Smith, E. E., Koeppe, R. A., Awh, E., Minoshima, S., Mintun, M. A. Spatial working memory in humans as revealed by PET. *Nature* **363,** 623–625, 1993.
24. Kwong, K. K., Belliveau, J. W., Chesler, D. A., Goldberg, I. E., Weisskoff, R. M., Poncelet, P., Kennedy, D. N., Hoppel, B. E., ???S., C. M., Turner, R., Cheng, H. M., Brady, T. J. and Rosen, B. R., Dynamic magnetic resonance of human brain activity during primary sensory stimulation. *Proceedings of the National Academy of Science*, 1992, **89,** 5675–5679.
25. McCarthy, G., Blamire, A. M., Puce, A., Nobre, A. C., Bloch, G., Hyder, F., Goldman-Rakic, P., Shulman, R. G. Functional magnetic resonance imaging of human prefrontal cortex during a spatial working memory task. *Proceedings of the National Academy of Sciences* **91,** 8690–8694, 1994.
26. Noll, D. C., Cohen, J. D., Meyer, C. H. and Schneder, W. Spiral K-space MR Imaging of cortical activation. *Journal of Magnetic Resonance Imaging* **5,** 49–56, 1995.
27. Pardo, J. V., Pardo, P. J., Janer, K. W., Raichle, M. E. The anterior cingulate cortex mediates processing selection in the Stroop atentional conflict paradigm. *Proceedings of the National Academy of Sciences U. S.A.* **87,** 256–259, 1990.
28. Petrides, M. E., Alivisatos, B., Meyer, E., Evans, A. C. Functional activation of the human frontal cortex during the performance of verbal working memory tasks. *Proceedings of the National Academy of Science U. S.A.* **90,** 878–882, 1993.
29. Posner, M. I. and Raichle, M. E., *Images of Mind.* Scientific American Library, New York, 1994.
30. Rosvold, H. E., Mirsky, A. F., Sarason, I., Bransome, E. D., Beck, L. H. A continuous performance test of brain damage. *Journal of Consulting Psychology* **20,** 343–350, 1956.
31. Savoy, R. L., Bandettini, P. A., O'Craven, K. M., Kwong, K. K., Davis, T. L., Baker, J. R., Weisskoff, R. M., Rosen, B. R. Pushing the temporal resolution of fMRI: Studies of very brief visual stimuli, onset variability and asynchrony, and stimulus-correlated changes in noise. *Society of Magnetic Resonance, Proceedings* **3,** 450, 1995.
32. Servan-Schreiber, D., Cohen, J. D. and Steingard, S. Schizophrenic deficits in the processing of context: A test of a theoretical model. *Archives of General Psychiatry* **53,** 1105–1112, 1996.
33. Smith, E. E., Jonides, J., Koeppe, R. A., Awh, E., Schumacher, E. H. and Minoshima, S. Spatial vs.

object working memory: PET investigations. *Journal of Cognitive Neuroscience* **7,** 337–356, 1995.
34. Talairach, J. and Tournoux, P., *Co-planar Stereotaxic Atlas of the Human Brain.* Thieme, New York, 1988.
35. Vazquez, A. L., Noll, D. C. Non-linear temporal aspects of the BOLD response in fMRI. *International Society of Magnetic Resonance in Medicine, Proceedings* **4,** 1765, 1996.
36. Wilson, F. A. W., Scalaidhe, S. P. O., Goldman-Rakic, P. S. Dissociation of object and spatial processing domains in primate prefrontal cortex. *Science* **260,** 1955–1957, 1993.
37. Woods, R. P., Cherry, S. R., Mazziotta, J. C. Rapid automated algorithm for aligning and reslicing PET images. *Journal of Computer Assisted Tomography* **16,** 620–633, 1992.
38. Woods, R. P., Mazziotta, J. C., Cherry, S. R. MRI–PET registration with automated algorithm. *Journal of Computer Assisted Tomography* **17,** 536–546, 1993.