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Prefrontal Contributions to Delayed Spatial and Object Alternation: A Positron Emission Tomography Study

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Delayed alternation tasks are frequently used as probes of frontal lobe functioning. To clarify the neural substrates of delayed alternation performance in humans, the authors measured regional cerebral blood flow with $H_2{}^{15}O$ positron emission tomography in healthy subjects as they performed delayed spatial and object alternation. Consistent with the monkey lesion literature, increased dorsolateral prefrontal activity emerged during delayed spatial alternation but not delayed object alternation, whereas orbitofrontal activations emerged in both alternation tasks. The possible cognitive processes contributing to the orbitofrontal and dorsolateral prefrontal involvement in delayed alternation are discussed. Additional activations localized to several nonfrontal regions suggest caution in interpreting alternation deficits in patients as strictly reflecting frontal lobe impairment.

Delayed alternation tasks have been widely used as probes of frontal lobe functions in both humans and animals. These tasks require subjects to select one of two objects on each trial, with the correct response corresponding to the object or location that the subject did not choose on the previous trial. Such tasks are typically conceptualized as working memory tasks because they require the subject to hold on line and update information on a trial-by-trial basis.

Several lesion studies in monkeys implicate the dorsolateral prefrontal cortex (DLPFC) as a critical substrate for performing delayed spatial alternations (DSA; Butters & Pandya, 1969; Goldman, Rosvold, Vest, & Galkin, 1971; Miller & Orbach, 1972; Mishkin, 1957; Mishkin, Vest, Waxler, & Rosvold, 1969; Stamm & Weber-Levine, 1971). Autoradiographic data in monkeys further confirm the engagement of the DLPFC in DSA (Friedman & Goldman-Rakic, 1994). The deficit in DSA that arises following DLPFC lesions is typically thought to reflect the specific involvement of the DLPFC in spatial working memory (Goldman et al., 1971; Goldman-Rakic, 1987). Selective lesions of the DLPFC do not typically impair performance of delayed object alternation (DOA) tasks (Mishkin & Manning, 1978; Mishkin et al., 1969). In contrast, deficits in both DSA and DOA often emerge following lesions to ventrolateral–lateral orbital regions along the inferior convexity (Butters, Butter, Rosen, & Stein, 1973; Miller & Orbach, 1972; Mishkin & Manning, 1978; Mishkin et al., 1969).

Despite their widespread use with animals, and increasing use as neuropsychological probes in humans (Freedman, 1990, 1994; Freedman, Black, Ebert, & Binns, 1998; Freedman & Oscar-Berman, 1986; Gross-Isseroff et al., 1996; Oscar-Berman, Zola-Morgan, Oberg, & Bonner, 1982; Zohar, Hermesh, Weizman, Voet, & Gross-Isseroff, 1999), only two published neuroimaging studies have examined the neural correlates of alternation tasks. Gold, Berman, Randolph, Goldberg, and Weinberger (1996) reported widespread orbitofrontal (OFC) and dorsolateral frontal activations in a hybrid task that combined elements of alternation and delayed response paradigms. However, the hybrid nature of the task makes it difficult to directly interpret these results with reference to standard DSA and DOA tasks. More recently, Curtis, Zald, Lee, and Pardo (2000) reported a positron emissions tomography (PET) study of object and spatial alternation performed with a minimal 1-s intertrial delay. Activations emerged in the medial orbital gyrus, inferior parietal lobule, and right anterior hippocampus during both the object and the spatial alternation conditions relative to a sensorimotor control task. This confirmed the

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involvement of the human OFC in alternation tasks. However, no significant activations emerged in the DLPFC region even during the spatial alternation condition. One possible cause for this lack of activation relates to the brief 1-s delay. Numerous studies in both animals and humans indicate the importance of delay length to the level of prefrontal involvement in various cognitive tasks (Fuster, 1989; Goldman-Rakic, 1987). Almost all studies of DSA in monkeys use 5-s delays. Interesting to note, Miller and Orbach (1972) observed that monkeys with DLPFC lesions can perform spatial alternations when there is no delay present, perform poorly when their view of the objects is transiently blocked (for less than a second), and perform even worse when their view of the objects is obstructed for 5 s between each trial. Given these data, which suggest a delay-dependent effect of DLPFC lesions on DSA performance, it seems reasonable to ask whether a DSA task with a 5-s delay engages the DLPFC in humans. To determine the neural correlates of DSA, we asked subjects to perform DSA while rCBF was estimated with $H_2{}^{15}O$ PET. For purpose of comparison, a small sample of subjects performed a DOA task while undergoing PET scanning.

Method

Subjects

Ten healthy volunteers (7 right-handed men and 3 right-handed women; mean age = 24 years, range = 20–29) participated in the DSA study. A separate group of 6 healthy subjects (4 right-handed men, 1 left-handed man, and 1 right-handed woman; mean age = 31 years, range = 21–45) participated in the DOA study. All subjects underwent a computerized psychiatric screening and were excluded if they demonstrated any current or past Axis I psychiatric disorders. Subjects also underwent a brief medical screening interview to rule out a history of neurological disorders. All subjects completed written informed consent approved by the Minneapolis Veterans Affairs Medical Center's Radioactive Drug Research Committee and Human Studies Committee.

Alternation Tasks

All tasks were presented using an IBM compatible personal computer, with a 37-cm diagonal monitor positioned approximately 50 cm in front of the subject's eyes. Figure 1 provides a schematic diagram of the DSA and DOA tasks. In both conditions, two-dimensional line drawings of 3-D objects appeared on a computer monitor. The specific objects were selected because they possessed visual features that were easy to distinguish from each other but did not lend themselves to verbal labeling. To select an object, subjects controlled a cursor with the use of a stylus and touch pad, which functioned like a mouse. The cursor position returned to a central point after each response to prevent the use of the cursor's position from the preceding trial as a cue on the current trial. Automated software recorded all subject responses to determine accuracy and adherence to task demands. Once subjects indicated their response, the objects were left on the screen for an additional 1 s accompanied by the word *correct* (colored green) or *incorrect* (colored red). On the first trial, the subject's choice was counted correct regardless of the subject's selection. The position of the two objects changed across trials according to a Gellermann randomization schedule (Gellermann, 1933). In both the DSA and the DOA tasks, a 5-s delay was interposed between trials during which time the screen remained dark, except for a fixation point that subjects were instructed to fixate on at all times. Prior to scanning, all subjects were informed of the rule that governs correct performance, and they practiced performing the tasks to a criterion of five consecutively correct trials. The control condition for both the DSA and the DOA consisted of stimuli presented in the exact same format as in the DSA and DOA conditions, except that on each trial a 10-point–font asterisk was embedded randomly on one of the two figures. Subjects were instructed to choose whichever object contained the asterisk. Scan order was approximately counterbalanced across the alternation and sensorimotor control conditions. Because one of our motivations was to examine areas becoming active (or showing more activity) with increasing delay demands, we also collected data while subjects performed spatial alternation with a 1-s delay (SA-1s). Nine subjects received both DSA and SA-1s conditions (each of these subjects was included as part of a previous report on SA-1s; Curtis et al., 2000). These subjects additionally received a separate sensorimotor control condition with 1-s intertrial delay (as opposed to the 5-s intertrial delay used for the DSA and DOA tasks).

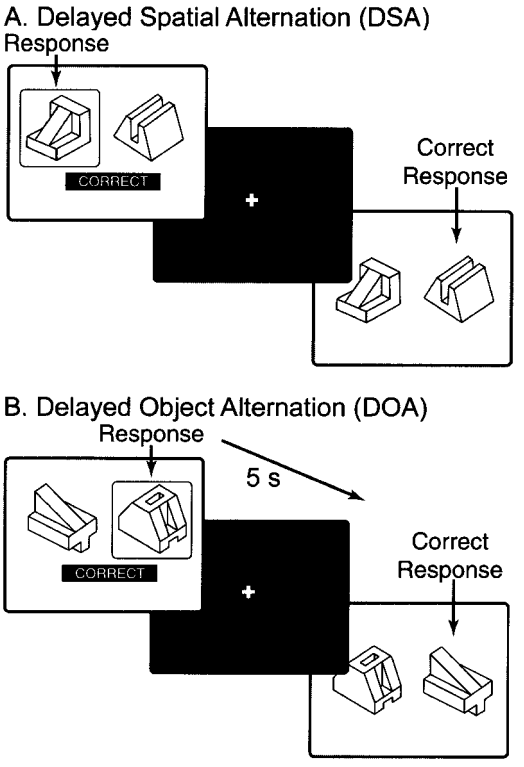

Figure 1. Schematic illustration of the DSA (top) and DOA (bottom) tasks. For each trial during the DSA condition, subjects selected the spatial location that was not chosen on the preceding trial, regardless of the object at that location. During the DOA condition, subjects selected the object that was not chosen on the preceding trial, regardless of its location.

PET Imaging and Analysis

Regional cerebral blood flow (rCBF) was estimated from tissue radioactivity using a Siemens ECAT 953B camera (Siemens, Knoxville, TN) with septa retracted, a slow-bolus injection of

$H_2{}^{15}O$ (0.25 mCi/kg infused at a constant rate over 30 s; Silbersweig et al., 1993), a 90-s scan acquisition, and a 10-min interscan interval. Scanning began with radiotracer arrival into the brain, which was timed to occur during the second to third trial of the task condition. Images were reconstructed using a 3-D reconstruction algorithm with a Hanning filter (0.5 cycles/pixel; Kinahan & Rogers, 1989) and were corrected for attenuation with a measured two-dimensional transmission scan. Measured coincidences were corrected for random detections and electronic dead time, but no corrections were made for decay or scatter. Normalization for global activity (1,000 counts), coregistration within each study session, placement of the intercommissural line from image fiducials, nonlinear warping of each subject's scans to a reference stereotactic atlas (Talairach & Tournoux, 1988), and statistical analyses were accomplished with software developed and provided by Minoshima and coworkers (Minoshima, Berger, Lee, & Mintun, 1992; Minoshima, Koeppe, Frey, & Kuhl, 1994; Minoshima et al., 1993). Images were blurred with a 6.0-mm 3-D gaussian filter, producing a final image resolution of 10-mm full width at half maximum. We adopted a significance threshold of $p < .0001$ on the basis of previous studies of the rate of false positive foci arising in bootstrapping analysis (Zald, Lee, Fluegel, & Pardo, 1998). Statistics reflect the maximum magnitude of rCBF increase in a given region relative to the global variance of all pixels within the brain (Worsley, Evans, Marrett, & Neelin, 1993). Identification of cerebellar foci used the atlas of Schmahmann, Doyon, Toga, Petrides, and Evans (2000), whereas identification of orbital foci followed the nomenclature and probability maps of Chiavaras, LeGoualher, Evans, and Petrides (2001) and the cytoarchitectural nomenclature of Ongur and Price (2000).

Results

All subjects performed the DSA tasks at 100% accuracy. Table 1 displays the results of the contrast between the DSA condition and the sensorimotor control task. Consistent with the lesion literature, performance of the DSA task was associated with significantly increased rCBF in a portion of the dorsolateral prefrontal cortex (middle frontal gyrus, BA 9, see Figure 2A). As can be seen from Figure 2, this activation represents a discrete focus that appears strictly lateralized to the left hemisphere. Another discrete focus emerged in the left posterior orbital gyrus (see Figure 2B). Unexpectedly, the largest volume focus localized to the precuneus region (Figure 2C). In 2 subjects, this focus lay near the edge of the PET camera's field of view. Because this could result in interpolation errors during 3-D image reconstruction, we reanalyzed the data without these subjects. However, this did not substantially alter the location or magnitude of the focus. Finally, an additional cluster of foci localized to the superior frontal gyrus.

Table 1
Delayed Spatial Alternation—Sensorimotor Control

Area	Talairach coordinate			*Z* score
Posterior orbital gyrus (BA 13,47/12m), L	−24,	17,	−20	3.8
Superior frontal gyrus (BA 6), L	−19,	10,	52	3.8
Precuneus (BA 7), L	−12,	−46,	50	3.8
Precentral gyrus (BA 4), R	46,	−6,	40	3.7
Middle frontal gyrus (BA 9), L	−28,	30,	32	3.5
Superior frontal gyrus (BA 6), R	6,	−17,	54	3.5
Precuneus (BA 7), R	1,	−44,	40	3.4
Superior frontal gyrus (BA 6), L	−17,	−8,	45	3.3

Note. BA = Brodmann's area; L = left; R = right.

The present data suggest performing DSA engages a discrete portion of the DLPFC, whereas previous data did not indicate activation of the DLPFC at a 1-s delay. To more carefully examine this difference, we performed a region-of-interest analysis comparing activations in the DSA condition (relative to the sensorimotor control condition) with activations emerging during the SA-1s condition (relative to a sensorimotor condition using a 1-s delay). We limited this analysis to 9 subjects who completed both the DSA condition and the briefer SA-1s condition to ensure that differences did not arise as a consequence of using different samples. A 2-pixel radius spherical region of interest was centered on the peak coordinate of the DLPFC activation in the DSA-sensorimotor control contrast and on the corresponding position in the 1-s spatial alternation–sensorimotor (1-s intertrial delay) contrast. In the DSA condition, rCBF increased by a mean of 8.1% ($SD = 5.5\%$) across the region of interest, whereas rCBF showed no substantial change ($M = -1.2\%$, $SD = 5.9\%$) in the SA-1s contrast. This greater activity occurred despite the fact that there were almost four times more trials in the SA-1s condition than in the DSA condition, $t(8) = 4.39$, $p < .005$.

Subjects performed the DOA task with reasonable accuracy ($M = 97.0\%$, $SD = 5.0\%$). Table 2 displays the contrast between the DOA and sensorimotor control task. Activations emerged in the left OFC (see Figure 3), anterior insula, supramarginal gyrus, and cerebellum. As in the Curtis et al. (2000) study of SA-1s, and consistent with data from animal lesions studies, no activations emerged in the DLPFC.

Discussion

The present data indicate that performance of DSA is associated with activation of the DLPFC in humans. This finding converges with the nonhuman primate literature, which indicates that lesions of the DLPFC impair the performance of DSA (Butters & Pandya, 1969; Miller & Orbach, 1972; Mishkin, 1957; Mishkin et al., 1969; Stamm & Weber-Levine, 1971), and performance of DSA induces increased glucose use in the DLPFC of nonlesioned animals (Friedman & Goldman-Rakic, 1994).

Given the greater DLPFC activity in the DSA task relative to the SA-1s condition, it seems tempting to speculate that this activity specifically relates to the greater mnemonic demand of the task. On the surface, such an interpretation appears consistent with both the animal literature on DSA (Goldman et al., 1971; Miller & Orbach, 1972) and theoretical conceptualizations about the importance of the DLPFC to spatial working memory (Goldman-Rakic, 1987). Furthermore, Sweeney et al. (1996) observed an activation in a fairly similar region of the left middle frontal gyrus (MFG) in a spatial oculomotor delayed response task. However, several factors temper this interpretation. First,

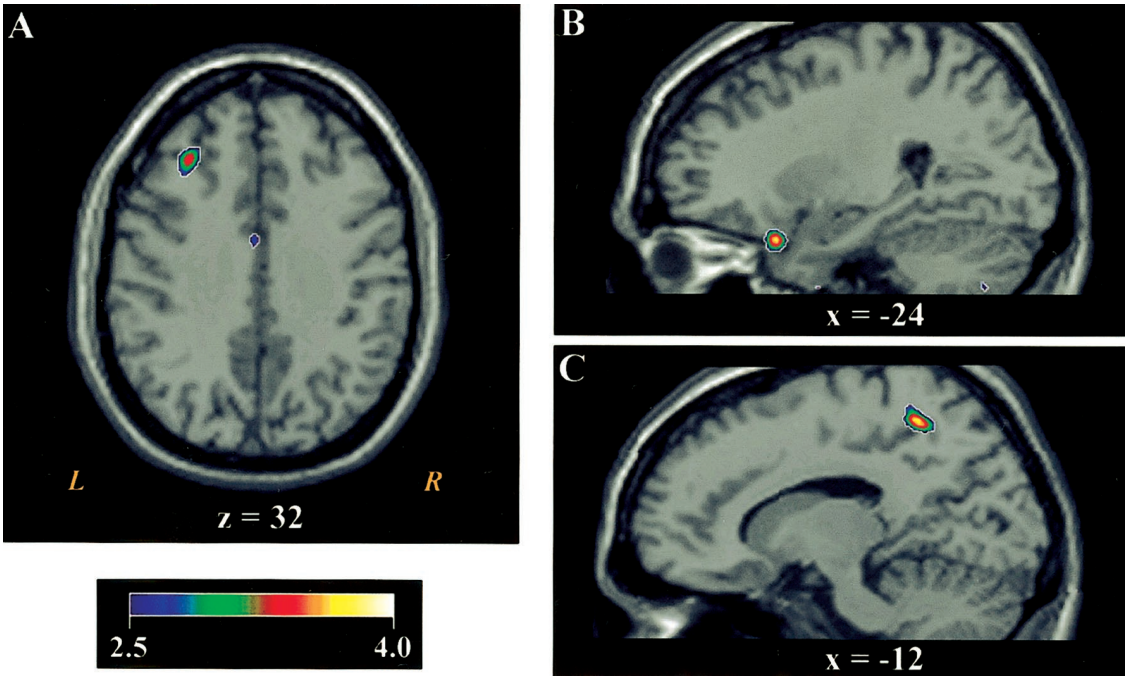

Figure 2. Areas of increased regional cerebral blood flow during delayed spatial alternation relative to the sensorimotor control. A: Transverse slice displaying the middle frontal gyrus focus at $z = 32$. B: Sagittal slice displaying the posterior orbital focus at $x = -24$. C: Sagittal slice displaying the precuneus focus at $x = -12$. All figures were produced by resampling the positron emission tomography *Z*-score image to a 1-mm^3 pixel resolution and templating the data to display only *Z* scores greater than 2.5 and by overlaying the resulting data on a high-resolution Talairach warped anatomical magnetic resonance image. *Z* scores are color coded according to the color bar at the bottom left side of the figure. L = left; R = right.

the left MFG has not emerged as a significant focus of activation in numerous other spatial working memory studies (see D'Esposito et al., 1998, for review). This portion of the left MFG or regions proximal to it have sometimes emerged in tasks involving the monitoring of auditory, verbal, or nonspatial visual information in working memory (Braver et al., 1997; Petrides, Alivisatos, Meyer, & Evans, 1993; Schumacher et al., 1996; Smith, Jonides, & Koeppe, 1996; Zatorre, Evans, & Meyer, 1994). Thus, to the extent that the focus is attributable to working memory, it does not appear to specifically reflect spatial working memory per se. Indeed, it should not be assumed that the activity reflects the maintenance of sensory information (either in terms of a spatial code or a left–right verbalization) during the delay period. Instead, the activation may reflect motor preparation because subjects know the location of the next correct response throughout the entire delay. Thus, to perform the DSA task, one can maintain either a retrospective representation of the sensory information (i.e., the object) or a prospective representation of the upcoming motor command. In a study of DLPFC activity during the delay period of delayed response tasks, Quintana and Fuster (1992) observed cells in the DLPFC whose activity was linked to the direction of a postdelay motor response (see also Rainer, Rao, & Miller, 1999). In other words, these cells show activity related to motor preparation as opposed to holding sensory information on line. The importance of the DLPFC for motor preparation in delayed responses tasks has been confirmed in studies of patients with frontal lesions (Ferreira et al., 1998) and in functional magnetic resonance imaging (fMRI) investigations with healthy subjects (D'Esposito, Ballard, Zarahn, & Aguirre, 2000; Pochon et al., 2001). The left lateralization of the observed DLPFC activity in the present study might thus relate to a right-hand motor preparation in the present study (all subjects responded with their right hand). The motor preparation issue might also explain why a similar DLPFC activation did not

Table 2
Delayed Object Alternation—Sensorimotor Control

Area	Talairach coordinate	*Z* score
Cerebellum (Lobule V), R	12, −58, −18	3.7
Medical orbital sulcus (BA 11), L	−21, 39, −9	3.7
Anterior insula, L	−30, 14, −2	3.4
Supramarginal gyrus (BA 40), L	−53, −49, 36	3.3

Note. R = right; BA = Brodmann's area; L = left.

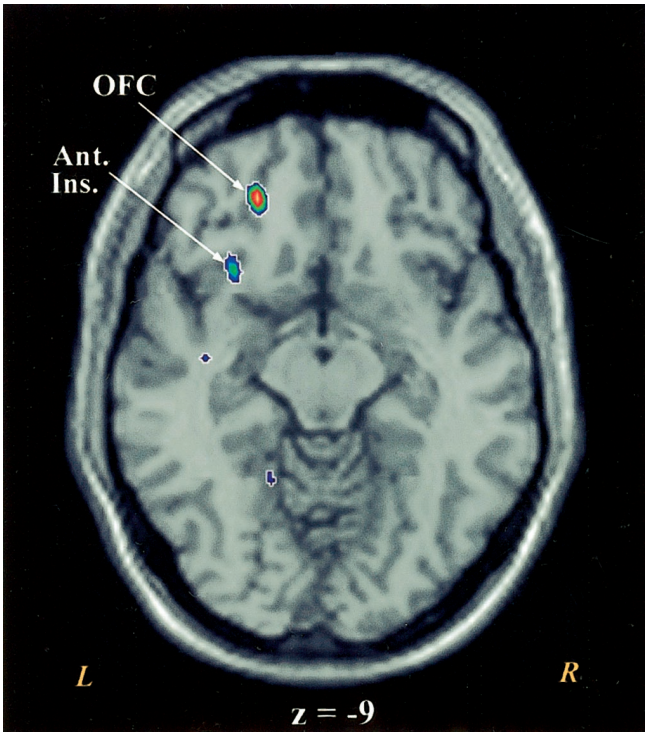

Figure 3. Areas of increased regional cerebral blood flow during delayed object alternation relative to the sensorimotor control. The figure displays a transverse slice at $z = -9$. The more anterior focus (marked OFC) falls within the medial orbital gyrus. The inferior end of the focus, falling within the anterior insula (marked Ant. Ins.), also appears in this figure. L = left; R = right.

emerge in the DOA task because in the DOA task subjects do not know which direction to move until the objects are represented after the delay period.

In considering the present result, it may also prove useful to compare the DLPFC result with findings in the Gold et al. (1996) study of a hybrid delayed response alternation task. The observed DLPFC focus in the present study appears quite close to activations reported by Gold et al. (e.g., x = −34, $y = 24$, $z = 28$). However, the activation in the present study involved only a discrete area of the frontal lobe, whereas Gold et al. observed widespread activity throughout the frontal lobes in both hemispheres. On the surface, this might suggest that Gold et al.'s task produced far more widespread and robust activation of the DLPFC and might make a better probe of frontal lobe functions. However, this speculation is tempered by Gold et al.'s observation that activity within the frontal lobe was substantially lower when subjects performed the task a second time. This second performance is more equivalent to the experience level of subjects in our study because our subjects had already practiced the task prior to scanning. The more restricted nature of delayed alternation activations following practice suggests that patients with DLPFC may show deficits in this type of task when the task is novel. In contrast, we would predict that lesions of the DLPFC would not impair performance of alternation tasks once the subject has learned the task rule and practiced applying it. Even lesions encompassing the MFG region in which we observed task-related activity in the present study may not impair DSA because subjects can adopt the alternate strategy of remembering stimulus features (spatial location) instead of using a motor preparation strategy. This reasoning provides a clearly testable hypothesis for studies with patient populations.

The lack of DLPFC activation in the DOA condition converges with the animal literature, which indicates that DOA performance remains intact following DLPFC lesions (Mishkin & Manning, 1978; Mishkin et al., 1969). However, it should be noted that this finding contrasts with an autoradiographic study by Friedman and Goldman-Rakic (1994) in which local cerebral glucose use was enhanced in the principal sulcus during both a DSA task and a DOA task. Two notable aspects of the Friedman and Goldman-Rakic study stand out and may help to explain why these authors obtained results that contrast with the lesion literature and the present results. First, the autoradiographic study used a 12-s delay, whereas the lesion literature and the present study used a shorter 5-s delay. Given that we have already provided evidence that delay length (1 s vs. 5 s) influences rCBF patterns during DOA, we cannot rule out the possibility that delay length plays a role in determining DLPFC recruitment during DOA. However, such a possibility seems inconsistent with much of the current human and nonhuman primate literature on object working memory. The second notable aspect of the Friedman and Goldman-Rakic study relates to the relatively large number of errors made by their subjects. Errors on this type of task in monkeys typically involve spatial intrusions (i.e., responses consistent with spatial alternation; Friedman & Goldman-Rakic, 1994; Mishkin & Manning, 1978). Thus, the high error rates may indicate that the subjects frequently reverted to DSA-like strategies. Such intrusions would clearly contaminate the ability to discriminate the results from those obtained during a DSA task. This stands in contrast to the almost perfect DOA performance of subjects in the present study.

The present data confirm the involvement of the OFC in both DOA and DSA, which is consistent with both Curtis et al.'s (2000) study using briefer 1-s delays as well as the monkey lesion literature. A few comments are warranted about the exact location of these activations. First, the foci appear to represent a more medial portion of the OFC than might be expected from the effects of lesions in monkeys, which often involve more lateral OFC–inferior convexity regions. Second, the exact location of these foci appears different than in Curtis et al.'s reported 1-s delay study. The reason for this shift remains unclear but may be the result of individual differences in structural or functional anatomy that are not completely resolved in the process of normalization to a common stereotactic space. Future studies using individual subject analysis of fMRI data may help to clarify these issues.

It is difficult to directly compare the present results with the sparse literature on human patients with frontal lobe

lesions (Freedman et al., 1998; Freedman & Oscar-Berman, 1986). These studies have examined the error rates of patients while they acquire the task. Because the subjects are not explicitly told the alternation rule in these studies, the deficits may reflect a reasoning deficit rather than a specific deficit in the ability to perform the task. This contrasts with the present PET study in which we examined subjects after they acquired and practiced the task rule. Nevertheless, it is notable that Freedman and Oscar-Berman (1986) observed the greatest deficits in both DSA and DOA acquisition when lesions included the OFC. Freedman et al. (1998) noted DOA acquisition impairments following both ventrolateral–orbitofrontal and more medial frontal (Brodmann areas 10, 24, and 32) lesions. Given the lack of medial frontal activations in the present study, it seems plausible that the more medial frontal regions observed by Freedman et al. (1998) reflect aspects of task acquisition rather than performance of already learned alternations.

The present study does not attempt to decompose the cognitive functions leading to OFC involvement in alternation tasks. Mishkin (1964) speculated that the OFC's contribution to alternation tasks relates to the need to inhibit a prepotent response (which would be to respond to the stimulus that was rewarded on the previous trial). However, once the subject has learned the task (as is the case in the present study), it is not clear that such an inhibition remains necessary. Specifically, the prepotency of the win–stay strategy is reduced after the subject has practiced the alternation strategy. Subjects do not describe having to specifically inhibit an urge to respond to the previously correct response instead of alternating between stimuli. An alternative explanation focuses on the hypothesis that the OFC participates in updating and holding on-line information about the relationship between stimuli and rewards (Zald & Kim, 2001). In many memory tasks, subjects need only hold a representation of whether or not they have seen a stimulus before or which of two stimuli has ever been associated with a reward. However, in the alternation paradigm, both stimuli are seen an equal number of times and rewarded an equal or almost equal number of times. Because of this, the ability to update and hold information on line regarding the last stimulus–reward pairing may take on particular importance in the performance of alternation tasks. Of course, for this hypothesis to possess explanatory power in the present study requires the assumption that the knowledge of being correct acts as a reward. Such an assumption requires testing, although it is consistent with the recent data implicating the OFC in the coding of abstract reward (O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001). A final hypothesis revolves around the possible role of the OFC in reducing interference. Data from humans with frontal leucotomies indicate that the OFC lesions preferentially affect tests of memory under conditions of high interference (Stuss et al., 1982). Alternation tasks involve high levels of proactive interference in that irrelevant memories of prior trials other than the immediately preceding trial can compete with the relevant memory of the past trial and interfere with correct performance. Indeed, subjects frequently report that the hardest part of the task is distinguishing their last response from earlier responses. Thus, it may be speculated that the OFC contributes to alternation tasks by reducing the effects of proactive interference. However, until studies examine the role of the OFC in specific task subcomponents such as interference suppression and working memory for reward, it will remain difficult to determine the precise nature of the OFC contribution to alternation tasks.

The present findings suggest that marked differences in the neural network subserving performance of alternation tasks occur depending on the modality and delay period of the task. However, some caution is necessary in drawing this conclusion because of the use of different samples of subjects in the DSA and DOA conditions. This precluded use of a factorial design that would allow examination of the main effects of delay and modality. However, application of such a factorial design is problematic even if all subjects had completed all of the conditions. Specifically, there is a confound in examining the effect of delay because of the dramatically different number of trials in a scan period. Thus, a failure to observe a focus that emerged in the short delay condition may reflect a decreased signal because of the sparseness of the responses. However, the emergence of new areas such as the DLPFC, which were not seen in the shorter delay trials, likely relate to the increased delay time because they emerge despite the far fewer responses produced during the DSA condition compared with the SA-1s condition.

The extent to which nonfrontal regions show activations during alternation tasks represents a striking feature of the neuroimaging literature on alternation. Nonfrontal activations range from the hippocampus and parietal cortex at short delays to the precuneus, cerebellum, and supramarginal gyrus at longer delays. Although the activation of these areas appears to vary depending on the specific modality (object vs. spatial) or delay length (1 s vs. 5 s), their presence suggests a danger in conceptualizing performance on alternation tasks purely as a measure of frontal lobe functioning. Other working memory and frontal lobe tasks, although sensitive to frontal lobe lesions, rarely show exclusive specificity for frontal lobe damage (Anderson, Damasio, Jones, & Tranel, 1991; Bondi, Kazniak, Bayles, & Vance, 1993; Dudkin, Chueva, Makarov, & Orlov, 1999; Grafman, Jonas, & Salazar, 1990; Reitan & Wolfson, 1994, 1995). Instead, such tasks typically engage and depend on normal functioning within a distributed network of frontal, posterior, and subcortical brain regions (Casey et al., 1998; Chafee & Goldman-Rakic, 1998, 2000; Cohen et al., 1997; Friedman & Goldman-Rakic, 1994; Oliveri et al., 2001; Postle, Stern, Rosen, & Corkin, 2000; Rowe & Passingham, 2001). The present results suggest that the neural basis of delayed alternation involves similarly widely distributed networks.

References

Anderson, S. W., Damasio, H., Jones, R. D., & Tranel, D. (1991). Wisconsin Card Sorting Test performance as a measure of frontal lobe damage. *Journal of Clinical & Experimental Neuropsychology, 13,* 909–922.

Bondi, M., Kazniak, A. W., Bayles, K. A., & Vance, K. A. (1993). Contributions of frontal system dysfunction to memory and perceptual abilities in Parkinson's disease. *Neuropsychology, 7,* 89–102.

Braver, T. S., Cohen, J. D., Nystrom, L. E., Jonides, J., Smith, E. E., & Noll, D. C. (1997). A parametric study of prefrontal cortex involvement in human working memory. *Neuroimage, 5,* 49–62.

Butters, N., Butter, C., Rosen, J., & Stein, D. (1973). Behavioral effects of sequential and one-stage ablations of orbital prefrontal cortex in the monkey. *Experimental Neurology, 39,* 204–214.

Butters, N., & Pandya, D. N. (1969, September 19). Retention of delayed-alternation: Effect of selective lesions of the sulcus pricipalis. *Science, 165,* 1271–1273.

Casey, B. J., Cohen, J. D., O'Craven, K., Davidson, R. J., Irwin, W., Nelson, C. A., et al. (1998). Reproducibility of fMRI results across four institutions using a spatial working memory task. *Neuroimage, 8,* 249–261.

Chafee, M. V., & Goldman-Rakic, P. S. (1998). Matching patterns of activity in primate prefrontal area 8a and parietal area 7ip neurons during a spatial working memory task. *Journal of Neurophysiology, 79,* 2919–2940.

Chafee, M. V., & Goldman-Rakic, P. S. (2000). Inactivation of parietal and prefrontal cortex reveals interdependence of neural activity during memory-guided saccades. *Journal of Neurophysiology, 83,* 1550–1566.

Chiavaras, M. M., LeGoualher, G., Evans, A., & Petrides, M. (2001). Three-dimensional probabilistic atlas of the human orbitofrontal sulci in standardized stereotaxic space. *Neuroimage, 13,* 479–496.

Cohen, J. D., Perlstein, W. M., Braver, T. S., Nystrom, L. E., Noll, D. C., Jonides, J., & Smith, E. E. (1997, April 10). Temporal dynamics of brain activation during a working memory task. *Nature, 386,* 604–608.

Curtis, C. E., Zald, D. H., Lee, J. T., & Pardo, J. V. (2000). Object and spatial alternation tasks with minimal delays activate the right anterior hippocampus proper in humans. *Neuroreport, 11,* 2203–2207.

D'Esposito, M., Aguirre, G. K., Zarahn, E., Ballard, D., Shin, R. K., & Lease, J. (1998). Functional MRI studies of spatial and nonspatial working memory. *Cognitive Brain Research, 7,* 1–13.

D'Esposito, M., Ballard, D., Zarahn, E., & Aguirre, G. K. (2000). The role of prefrontal cortex in sensory memory and motor preparation: An event-related fMRI study. *Neuroimage, 11,* 400–408.

Dudkin, K. N., Chueva, I. V., Makarov, F. N., & Orlov, I. V. (1999). Short-term memory processes in delayed visual differentiation in rhesus macaques after bilateral removal of field 7 of the parietal cortex. *Neuroscience and Behavioral Physiology, 29,* 483–491.

Ferreira, C. T., Verin, M., Pillon, B., Levy, R., Dubois, B., & Agid, Y. (1998). Spatio-temporal working memory and frontal lesions in man. *Cortex, 34,* 83–98.

Freedman, M. (1990). Object alternation and orbitofrontal system dysfunction in Alzheimer's and Parkinson's disease. *Brain & Cognition, 14,* 134–143.

Freedman, M. (1994). Frontal and parietal lobe dysfunction in depression: Delayed alternation and tactile learning deficits. *Neuropsychologia, 32,* 1015–1025.

Freedman, M., Black, S., Ebert, P., & Binns, M. (1998). Orbitofrontal function, object alternation and perseveration. *Cerebral Cortex, 8,* 18–27.

Freedman, M., & Oscar-Berman, M. (1986). Bilateral frontal lobe disease and selective delayed response deficits in humans. *Behavioral Neuroscience, 100,* 337–342.

Friedman, H. R., & Goldman-Rakic, P. S. (1994). Coactivation of prefrontal cortex and inferior parietal cortex in working memory tasks revealed by 2DG functional mapping in the rhesus monkey. *Journal of Neuroscience, 14,* 2775–2788.

Fuster, J. M. (1989). *The prefrontal cortex.* New York: Raven Press.

Gellermann, L. W. (1933). Chance order of alternating stimuli in visual discrimination experiments. *Journal of Genetic Psychology, 42,* 207–208.

Gold, J. M., Berman, K. F., Randolph, C., Goldberg, T. E., & Weinberger, D. R. (1996). PET validation of a novel prefrontal task: Delayed response alternation. *Neuropsychology, 10,* 3–10.

Goldman, P. S., Rosvold, H. E., Vest, B., & Galkin, T. W. (1971). Analysis of the delayed-alternation deficit produced by dorsolateral prefrontal lesions in the rhesus monkey. *Journal of Comparative and Physiological Psychology, 77,* 212–220.

Goldman-Rakic, P. S. (1987). Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In F. Plum & V. Mountcastle (Eds.), *Handbook of physiology* (Vol. 5, pp. 373–417). New Haven, CT: Yale University School of Medicine.

Grafman, J., Jonas, B., & Salazar, A. (1990). Wisconsin Card Sorting Test performance based on location and size of neuroanatomical lesion in Vietnam veterans with penetrating head injury. *Perceptual and Motor Skills, 71,* 1120–1122.

Gross-Isseroff, R., Sasson, Y., Voet, H., Hendler, T., Luca-Haimovici, K., Kandel-Sussman, H., & Zohar, J. (1996). Alternation learning in obsessive-compulsive disorder. *Biological Psychiatry, 39,* 733–738.

Kinahan, P. E., & Rogers, J. G. (1989). Analytic 3-D image reconstruction using all detected events. *IEEE Transactions on Nuclear Science, 36,* 964–986.

Miller, M. H., & Orbach, J. (1972). Retention of spatial alternation following frontal lobe resections in stump-tailed macaques. *Neuropsychologia, 10,* 291–298.

Minoshima, S., Berger, K. L., Lee, K. S., & Mintun, M. A. (1992). An automated method for rotational correction and centering of three-dimensional functional brain images. *Journal of Nuclear Medicine, 33,* 1579–1585.

Minoshima, S., Koeppe, R. A., Frey, K. A., & Kuhl, D. E. (1994). Anatomic standardization: Linear scaling and nonlinear warping of functional brain images. *Journal of Nuclear Medicine, 35,* 1528–1537.

Minoshima, S., Koeppe, R. A., Mintun, M. A., Berger, K. L., Taylor, S. F., Frey, K. A., & Kuhl, D. E. (1993). Automated detection of the intercommissural line for stereotactic localization of functional brain images. *Journal of Nuclear Medicine, 34,* 322–329.

Mishkin, M. (1957). Effects of small frontal lesions on delayed alternation in monkeys. *Journal of Neurophysiology, 20,* 615–622.

Mishkin, M. M. (1964). Preservation of central sets after frontal lesions in monkeys. In J. M. Warren & K. Akert (Eds.), *The frontal granular cortex and behavior* (pp. 219–241). New York: McGraw-Hill.

Mishkin, M., & Manning, F. J. (1978). Non-spatial memory after selective prefrontal lesions in monkeys. *Brain Research, 143,* 313–323.

Mishkin, M., Vest, B., Waxler, M., & Rosvold, H. E. (1969). A re-examination of the effects of frontal lesions on object alternation. *Neuropsychologia, 7,* 357–363.

O'Doherty, J., Kringelbach, M. L., Rolls, E. T., Hornak, J., & Andrews, C. (2001). Abstract reward and punishment representations in the human orbitofrontal cortex. *Nature Neuroscience, 4,* 95–102.

Oliveri, M., Turriziani, P., Carlesimo, G. A., Koch, G., Tomaiuolo, F., Panella, M., & Caltagirone, G. M. (2001). Parieto-frontal interactions in visual-object and visual-spatial working memory: Evidence from transcranial magnetic stimulation. *Cerebral Cortex, 11,* 606–618.

Ongur, D., & Price, J. L. (2000). The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cerebral Cortex, 10,* 206–219.

Oscar-Berman, M., Zola-Morgan, S. M., Oberg, R. G., & Bonner, R. T. (1982). Comparative neuropsychology and Korsakoff's syndrome: III. Delayed response, delayed alternation and DRL performance. *Neuropsychologia, 20,* 187–202.

Petrides, M., Alivisatos, B., Meyer, E., & Evans, A. C. (1993). Functional activation of the human frontal cortex during the performance of verbal working memory tasks. *Proceedings of the National Academy of Sciences, USA, 90,* 878–882.

Pochon, J. B., Levy, R., Poline, J. B., Crozier, S., Lehericy, S., Pillon, B., et al. (2001). The role of dorsolateral prefrontal cortex in the preparation of forthcoming actions: An fMRI study. *Cerebral Cortex, 11,* 260–266.

Postle, B. R., Stern, C. E., Rosen, B. R., & Corkin, S. (2000). An fMRI investigation of cortical contributions to spatial and nonspatial visual working memory. *Neuroimage, 11,* 409–423.

Quintana, J., & Fuster, J. M. (1992). Mnemonic and predictive functions of cortical neurons in a memory task. *Neuroreport, 3,* 721–724.

Rainer, G., Rao, S. C., & Miller, E. K. (1999). Prospective coding for objects in primate prefrontal cortex. *Journal of Neuroscience, 19,* 5493–5505.

Reitan, R. M., & Wolfson, D. (1994). A selective and critical review of neuropsychological deficits and the frontal lobes. *Neuropsychology Review, 4,* 161–198.

Reitan, R. M., & Wolfson, D. (1995). Category test and trail making test as measures of frontal lobe functions. *Clinical Neuropsychologist, 9,* 50–56.

Rowe, J. B., & Passingham, R. E. (2001). Working memory for location and time: Activity in prefrontal area 46 relates to selection rather than maintenance in memory. *Neuroimage, 14,* 77–86.

Schmahmann, J. D., Doyon, J., Toga, A. W., Petrides, M., & Evans, A. C. (2000). *MRI atlas of the human cerebellum.* San Diego, CA: Academic Press.

Schumacher, E. H., Lauber, E., Awh, E., Jonides, J., Smith, E. E., & Koeppe, R. A. (1996). PET evidence for an amodal verbal working memory system. *Neuroimage, 3,* 79–88.

Silbersweig, D. A., Stern, E., Frith, C. D., Cahill, C., Schnorr, L., Grootoonk, S., et al. (1993). Detection of thirty-second cognitive activations in single subjects with positron emission tomography: A new low-dose $H_2{}^{15}O$ regional cerebral blood flow three-dimensional imaging technique. *Journal of Cerebral Blood Flow and Metabolism, 13,* 617–629.

Smith, E. E., Jonides, J., & Koeppe, R. A. (1996). Dissociating verbal and spatial working memory using PET. *Cerebral Cortex, 6,* 11–20.

Stamm, J. S., & Weber-Levine, M. L. (1971). Delayed alternation impairments following selective prefrontal cortical ablations in monkeys. *Experimental Neurology, 33,* 263–278.

Stuss, D. T., Kaplan, E. F., Benson, D. F., Weir, W. S., Chiulli, S., & Sarazin, F. F. (1982). Evidence for the involvement of orbitofrontal cortex in memory functions: An interference effect. *Journal of Comparative and Physiological Psychology, 96,* 913–925.

Sweeney, J. A., Mintun, M. A., Kwee, S., Wiseman, M. B., Brown, D. L., Rosenberg, D. R., & Carl, J. R. (1996). Positron emission tomography study of voluntary saccadic eye movements and spatial working memory. *Journal of Neurophysiology, 75,* 454–468.

Talairach, J., & Tournoux, P. (1988). *Co-planar stereotaxic atlas of the human brain.* New York: Thieme.

Worsley, K. J., Evans, A. C., Marrett, S., & Neelin, P. (1993). A three-dimensional statistical analysis for CBF activation studies in human brain. *Journal of Cerebral Blood Flow and Metabolism, 12,* 900–918.

Zald, D. H., & Kim, S. W. (2001). The orbitofrontal cortex. In S. Salloway, D. Duffy, & P. F. Malloy (Eds.), *The frontal lobes and neuropsychiatric illness* (pp. 33–70). Washington, DC: American Psychiatric Press.

Zald, D. H., Lee, J. T., Fluegel, K. W., & Pardo, J. V. (1998). Aversive gustatory stimulation activates limbic circuits in humans. *Brain, 121,* 1143–1154.

Zatorre, R. J., Evans, A. C., & Meyer, E. (1994). Neural mechanisms underlying melodic perception and memory for pitch. *Journal of Neuroscience, 14,* 1908–1919.

Zohar, J., Hermesh, H., Weizman, A., Voet, H., & Gross-Isseroff, R. (1999). Orbitofrontal cortex dysfunction in obsessive-compulsive disorder? I. Alternation learning in obsessive-compulsive disorder: Male–female comparisons. *European Neuropsychopharmacology, 9,* 407–413.

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