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# Frontal Lobe Activation During Object Alternation Acquisition

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Object alternation (OA) tasks are increasingly used as probes of ventral prefrontal functioning in humans. In the most common variant of the OA task, subjects must deduce the task rule through trial-and-error learning. To examine the neural correlates of OA acquisition, the authors measured regional cerebral blood flow with positron emission tomography while subjects acquired an OA task, performed a sensorimotor control condition, or performed already learned and practiced OA. As expected, activations emerged in the ventral prefrontal cortex. However, activation of the presupplemental motor area was more closely associated with successful task performance. The authors suggest that areas beyond the ventral prefrontal cortex are critically involved in OA acquisition.

Object alternation (OA) tasks are increasingly used as behavioral probes of ventral prefrontal functioning in humans (Abbruzzese, Bellodi, Ferri, & Scarone, 1995; Abbruzzese, Ferri, & Scarone, 1997; Cavedini, Ferri, Scarone, & Bellodi, 1998; Faraone et al., 1999; Freedman, 1990, 1994; Gansler, Covall, McGrath, & Oscar-Berman, 1996; Good et al., 2002; Koenen et al., 2001; Marie et al., 1999; Pantelis & Brewer, 1995; Seidman, Oscar-Berman, Kalinowski, & Ajilore, 1995; Zohar, Hermesh, Weizman, Voet, & Gross-Isseroff, 1999). In such tasks, subjects view two objects and on a trial-by-trial basis must select whichever object they did not select on the previous trial. The interpretation that OA deficits reflect dysfunction of the orbitofrontal cortex (OFC) or the neighboring ventrolateral prefrontal cortex (VLPFC) derives from lesion studies in monkeys that demonstrated marked deficits in OA performance following lesions to the lateral OFC (LOFC) and VLPFC (Mishkin & Manning, 1978; Mishkin, Vest, Waxler, & Rosvold, 1969; Oscar-Berman & Bardenhagen, 1998; Pribram & Mishkin, 1956). Similarly, in human subjects, lesions to ventral prefrontal regions have been observed to impair performance of OA tasks (Freedman, Black, Ebert, & Binns, 1998).

In considering the literature on OA tasks, one must distinguish between deficits in task acquisition and deficits in task performance. Once a subject learns the OA rule, performance is primarily influenced by the ability to update and maintain a representation in working memory of the last selected stimulus (or the last unselected stimulus) and an ability to maintain and apply the task rule to guide response selection. Freedom from distraction, the ability to inhibit the selection of the just-rewarded object, and minimization of anterograde interference from prior selections may additionally play a critical role in task performance (Curtis, Zald, Lee, & Pardo, 2000). However, most researchers studying OA assess the ability of subjects to acquire the task rather than examining practiced performance. For instance, in animal studies, the subjects are typically studied during task reacquisition following surgical removal of the cortex (Mishkin & Manning, 1978; Mishkin et al., 1969; Pribram & Mishkin, 1956). Obviously, the animals in these experiments cannot be explicitly told the rules, and they show no evidence of having retained the rules postsurgery. Studied in this state, the animals show a marked inability to reacquire the task rules, often showing no improvement after thousands of trials. In most studies of OA tasks in humans, the subjects are similarly not told the task rules and must deduce the rules through trial-and-error learning. A number of factors can hinder such trial-and-error learning, including impairments in deductive reasoning skills, an inability to inhibit prepotent responses, coding of task feedback (e.g., errors), freedom from perseveration, and working memory for trial outcomes (Bardenhagen & Bowden, 1998; Mishkin, 1964). Measures of both trials to criterion and total errors can reflect any of these acquisition factors, in addition to reflecting factors that impair performance after rule acquisition. Regardless of the source of the poor acquisition, patients with ventral prefrontal lesions appear slower than healthy individuals in acquiring accurate OA performance (Freedman et al., 1998).

We have previously reported data from positron emission tomography (PET) studies demonstrating that performance of OA tasks after rule acquisition induces selected areas of activation within the OFC, with additional involvement of several regions beyond the prefrontal cortex (Curtis et al., 2000; Zald, Curtis, Folley, & Pardo, 2002). In contrast, no neuroimaging studies have specifically reported data during the acquisition phase of an alternation task, when subjects were learning the task rule. The closest point of reference is a study by Gold and colleagues (Gold, Berman, Randolph, Goldberg, & Weinberger, 1996), in which subjects demonstrated widespread frontal activation during an unpracticed hybrid delayed-alternation/delayed-response task, with less activity arising during a second block of trials. However, the subjects had been explicitly told the task rule before they started the initial task. Another point of reference involves studies in which researchers have examined the cognitive processes likely

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to be necessary to acquire the OA task. These include processes associated with trial-and-error learning, formulating and testing hypotheses, using deductive reasoning, monitoring task feedback, and flexibly altering response strategies in response to errors. The inferior frontal gyrus and adjacent LOFC (Brodmann areas 45 and 47/12) have often emerged during neuroimaging studies involving deductive reasoning (Goel, Gold, Kapur, & Houle, 1997, 1998; Knauff, Mulack, Kassubek, Salih, & Greenlee, 2002) and hypothesis testing about task rules (Elliott & Dolan, 1998), findings that are consistent with the importance of the VLPFC–LOFC region in OA task acquisition in monkeys.

However, it is also clear that other frontal regions become active during similar conditions. For instance, the dorsolateral prefrontal cortex (DLPFC), the presupplemental motor area (pre-SMA; a.k.a. the superior frontal gyrus, pars medialis, or medial frontal gyrus), and the frontal pole have been variously observed to become activated during deductive reasoning tasks and tasks requiring rule learning and hypothesis testing (Elliott & Dolan, 1998; Goel et al., 1997; Knauff et al., 2002; Parsons & Osherson, 2001; Strange, Henson, Friston, & Dolan, 2001). Thus, there are a number of frontal regions outside of the VLPFC–LOFC that might be predicted to play a role during acquisition of an OA task. In the present study, we examined the pattern of cortical activation during trial-and-error acquisition of an OA task. Neural activity was assessed by measuring regional cerebral blood flow (rCBF) with $H_2{}^{15}O$ PET, allowing us to avoid the problems of susceptibility artifact and signal dropout associated with functional MRI (fMRI) measurements of ventral prefrontal regions. PET is also advantageous for this type of study in that robust blood flow changes can be observed during a single initial block of acquisition trials.

## Method

### Subjects

Eleven healthy volunteers were informed of the nature and risks associated with this experiment and provided written consent. The volunteers consisted of 7 right-handed men, 1 left-handed man, and 3 right-handed women with a mean age of 27 and an age range of 20–45 years. All were found to be free of major psychiatric illness on the basis of a brief computerized psychiatric screening inventory (Robins & Marcus, 1988). All subjects indicated that they had no history of neurological symptoms, were free of current medical problems, and were not taking any medications with significant psychotropic properties. All subjects completed written informed consent forms approved by the Radioactive Drug Research and Human Subject Committees of the Minneapolis Veterans Affairs Medical Center.

Because we were interested in imaging the acquisition of the alternation rule, subjects were excluded from all analyses if they reached criterion-level performance in less than 30 s, as a significant part of the scanning window would occur after they had discovered the rule. The criterion for learning was defined as five consecutive correct responses (the probability of obtaining five consecutive responses by chance is $p = .03$). One subject (a left-handed man) was excluded because he learned the task too quickly (amount of time taken to reach the criterion = 28 s, total number of incorrect responses = 2, and number of trials required to reach the criterion = 9).

In addition, we performed a second analysis restricted to subjects who demonstrated successful learning of the task rule. We performed this second analysis to (a) define areas that activate during successful rule learning and to (b) provide confidence that the results reflected active involvement in attempting to solve the task (which could not be verified in subjects who did not acquire the task rule). Three subjects were excluded from this second analysis because they failed to learn the task within the time or trial limit. One additional subject was excluded who failed to reach the criterion but who was unfortunately stopped prior to the discontinuation trial–time limit (the subject was included in the initial analysis because discontinuation did not occur until after the completion of the scan period). This left a total of 6 subjects who met the inclusion criteria for the second analysis. Of these 6 subjects, 4 were men, 2 were women, all were right-handed, and their mean age was 24.5 years (range = 20–35 years).

### Task Design

Subjects performed three computerized tasks that were matched for sensory features and motor demands. Tasks were presented on a 37-cm diagonal computer screen positioned 50 cm in front of the subjects' eyes. During each scan, two novel three-dimensional line drawings of objects were presented, with their position determined according to a Gellermann randomization schedule (Gellermann, 1933). As illustrated in Figure 1, the two objects were easily distinguishable, and neither stimulus could be readily described verbally. To select an object, subjects moved a cursor using a stylus and touch pad. The cursor position returned to a central position following each trial to prevent the use of the cursor's position on the previous trial as a visual cue on the current trial. For feedback, either the word *correct* in a green font or the word *incorrect* in a red font appeared on the screen with the objects for 1 s following each object selection. This was followed by a 1-s interstimulus interval during which the screen went dark, except for a fixation cross in the center of the screen. The subject's first response was scored as correct, regardless of which object was selected. On trials following an incorrect response, the object that would have been correct on the previous trial continued to be the correct object until the subject selected it. On such trials, the positions of the two objects continued to vary according to the Gellermann randomization schedule. Note that this procedure is different from that used in many OA acquisition studies, which keep the position of objects the same on all trials following correct responses. Although this difference appears subtle, it likely has a significant impact on the difficulty of deducing the task rule. Specifically, when correction trials remain static in position, it becomes more quickly apparent that position is not a factor, and hence the subject may more easily deduce the object-based rule. This is not the case when positions are randomly determined on correction trials. Thus, OA

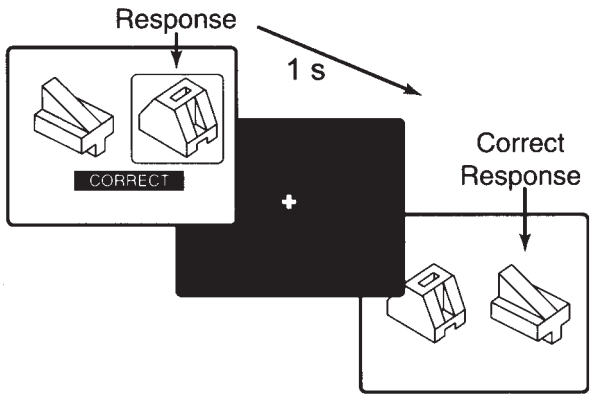


*Figure 1.* Schematic illustration of the object alternation (OA) task. The correct response in the OA task is the object that was not chosen in the previous trial, regardless of its position. The OA acquisition condition and OA practiced condition were identical except for subjects' knowledge of the rule and prior exposure to the task. The sensorimotor control condition looked identical except for the presence of an embedded asterisk indicating which object to choose on each trial.

acquisition tasks that use random positioning on correction trials (as we use in this study) are likely to produce a higher average number of trials to reach criterion and more failures to reach criterion than are studies using static positioning on correction trials.

In the OA acquisition (OAacq) condition, subjects were instructed that they had to figure out the rule determining which item was correct on each trial. Subjects were discontinued between the 50th and 60th trial (typically after the first incorrect response after the 49th trial). For purposes of statistical reporting and analyses, we placed a cap at the 55th trial (which would have been the earliest that any of the subjects who had yet to acquire the task rule could have acquired it if they continued after the 50th trial). We used this cap to prevent any differences in the precise discontinuation point after the 50th trial from influencing the results. Similarly, incorrect responses occurring after the 50th trial were not included in the descriptive statistics or entered into correlation analyses. In the practiced OA (OApract) condition, subjects performed OA tasks after having been explicitly told the task rule and after having practiced applying the task rule for 2 min. In the sensorimotor control (SMC) conditions, a 10-point font asterisk was randomly embedded in one of the two objects on each trial. Subjects were instructed to select whichever object had the asterisk in it. The OAacq and SMC conditions were counterbalanced, as were the OApract and SMC conditions. In contrast, the OAacq condition always preceded the OApract condition so that we could ensure that subjects were blind to the task rule. In the OAacq condition, subjects began the task a few seconds prior to the start of scan acquisition so that they were engaged in the task but had not yet completed more than a couple of trials at the start of the scan period. In the two other conditions, tasks were begun approximately 10 s prior to the start of scan acquisition.

### PET Imaging and Analysis

We assessed rCBF using a Siemens ECAT 953B scanner (Siemens, Knoxville, TN) with septa retracted. The 953B scanner provides 31 slices at 3.4-mm thickness, with an approximate inherent transverse and axial resolution of 5.8 and 4.4 mm, respectively, at full width at half maximum (Mazoyer, Trebossen, Deutch, Casey, & Blohm, 1991). Subjects received a slow-bolus, constant-rate injection of $H_2{}^{15}O$ (0.25 millicuries [mCi]/kg; e.g., a 17.5-mCi [648-megabecquerel (MBq)] injection for a 70-kg person) and a 90-s scan acquisition. Subjects were placed in the scanner to provide optimal visualization of the ventral prefrontal regions; as a result, the most superior aspects of the frontal and parietal lobes were out of the field of view. We reconstructed images with filtered back projection using attenuation correction from a 6-min transmission scan. Rotations to the intercommissural plane, normalization for whole brain activity, intra- and intersubject coregistration, and nonlinear warping to Talairach space (Talairach & Tournoux, 1988) were accomplished with software developed by Minoshima and colleagues (Minoshima, Berger, Lee, & Mintun, 1992; Minoshima, Koeppe, Frey, & Kuhl, 1994; Minoshima et al., 1993). Images were resampled to 2.25-$mm^3$ isovoxels and filtered with a 3-pixel, three-dimensional Gaussian filter producing a final image resolution of 9 mm at full width at half maximum prior to group statistical analysis. For analysis, we used a significance threshold of $p = .0005$ (equivalent to a $z$ score of 3.3) that was based on previous studies of the rate of false-positive foci arising in a bootstrapping analysis (Zald, Lee, Fluegel, & Pardo, 1998). For statistical analysis, we used the global variance of all intracerebral pixels (Worsley, Evans, Marrett, & Neelin, 1992). Cytoarchitectural (Brodmann area) labeling followed the Talairach Atlas (Talairach & Tournoux, 1988), except for ventral prefrontal regions, for which we based the cytoarchitectonic boundaries and labeling on the parcellation scheme of Öngür, Ferry, and Price (2003).

For correlation analyses between task performance and rCBF change, we used regions of interest with a 2-pixel (4.5-mm) radius sphere. As noted previously, 1 subject did not have complete behavioral data because he discontinued the task prematurely. This subject was excluded from the correlation analyses, leaving 9 subjects and eight degrees of freedom for those analyses.

## Results

### Behavioral Data

Of the 10 subjects included in the primary analysis, 6 subjects reached the criterion of five consecutive correct responses, whereas 4 subjects failed to reach the criterion. The mean number of incorrect responses at the point in which subjects reached criterion or the task was discontinued because of failure to reach criterion was 19 (range = 5–32). The 6 subjects who successfully deduced the task rule took, on average, 34 trials to reach the criterion (range = 18–54). For this group, the number of incorrect responses ranged from 5 in the fastest learner to 26 in the slowest learner ($M = 16$).

### Imaging Results

Table 1 displays the peak response in the OAacq condition relative to the SMC condition for all of the subjects. The most prominent peak in the frontal lobe localized to the VLPFC in the inferior frontal gyrus, pars orbitalis ($IFG_{orb}$; see Figure 2). Additional frontal lobe activation emerged in the left dorsal superior frontal gyrus, pars medialis, in the area defined as the pre-SMA by Picard and Strick (1996). Similarly, a posterior portion of the middle frontal gyrus demonstrated increased activity. More ventrally, there were trends toward activation in the inferior frontal pole ($x = -6$, $y = 55$, $z = -18$; $z$ score = 3.2), the ventral medial wall ($x = 3$, $y = 3$, $z = -16$; $z$ score = 3.2), and the medial orbital gyrus ($x = 15$, $y = 39$, $z = -16$; $z$ score = 3.1), but these failed to reach full statistical significance.

Table 2 displays the peak areas of activation during OAacq relative to the SMC condition in the 6 subjects who successfully acquired the task rule within the trial–time discontinuation limit. This analysis provides a greater level of interpretational specificity because it is limited to subjects who successfully used the cognitive processes necessary to solve the task. The pre-SMA emerged as the most significant peak in this analysis (see Figure 3). The right $IFG_{orb}$ again arose as a significant area of activation. The

Table 1
*OA Acquisition: Sensorimotor Control (n = 10)*

| Area | Coordinates | $z$ score |
|---|---|---|
| Frontal lobe | | |
| Right inferior frontal gyrus (pars orbitalis; BA 47/12) | 30, 44, −7 | 3.6 |
| Left middle frontal gyrus (BA 8) | −37, 14, 36 | 3.4 |
| Left pre-SMA (BA 6) | −6, 10, 45 | 3.3 |
| Posterior regions | | |
| Cerebellum (lobule VII) | 8, −71, −29 | 3.4 |

*Note.* Talairach stereotactic coordinates in millimeters: $x$ = medial–lateral relative to midline (+ = right hemisphere); $y$ = anterior–posterior relative to the anterior commissure (+ = anterior); $z$ = inferior–superior relative to intercommissural plane (+ = superior). Peak areas of activation had $z$ scores above 3.3 and exceeded a threshold of $p = .0005$. OA = object alternation; BA = Brodmann area; pre-SMA = presupplemental motor area.

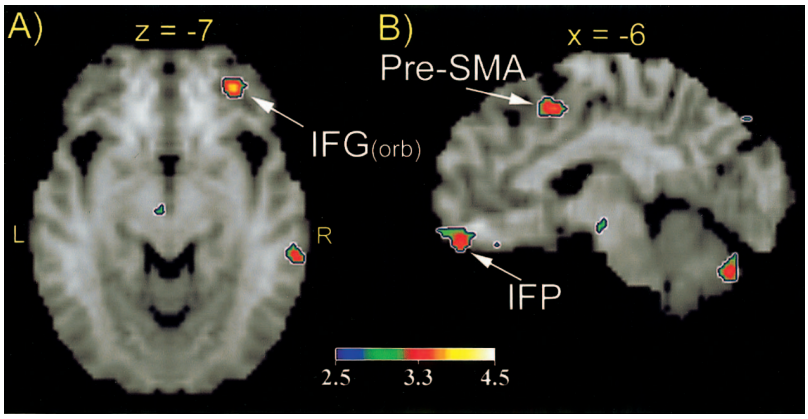


*Figure 2.* Activation during the object alternation acquisition condition relative to the sensorimotor control condition in 10 subjects. A: Inferior frontal gyrus, pars orbitalis ($IFG_{orb}$). A small nonsignificant focus ($z$ score = 3.2) can also be seen in the right middle temporal gyrus. B: Presupplemental motor area (pre-SMA) and inferior frontal pole (IFP). A focus can also be seen in the cerebellum, but it falls at the boundary of the field of view. The positron emission tomography $z$-score maps were thresholded to show activations above a threshold of $p < .005$, approximately equivalent to a $z$ score of 2.5. The threshold for statistical significance was set at $p < .0005$, equivalent to a $z$ score of 3.3. L = left; R = right.

inferior frontal pole along the frontomarginal gyrus (which had shown only a trend in the initial analysis) now reached statistical significance. An additional activation also emerged in the middle frontal gyrus in a more superior and lateral section of the frontal pole (close to the boundary between Brodmann areas 10 and 46). Outside the frontal lobe, the strongest activations localized to a portion of the right middle temporal gyrus and the left parietal–occipital transition area (both of these areas had shown significant trends, $p < .001$, in the primary analysis of all 10 subjects, but had fallen slightly below statistical significance).

Given the greater magnitude of activations in several brain regions when the analysis was restricted to subjects who successfully solved the task, we wondered whether any of these regions might be differentially associated with task performance. To test this possibility, we ran correlation analyses between task performance measures (number of trials required to reach the criterion or discontinuation and number of incorrect responses when reaching the criterion or discontinuation) and percentages of rCBF change between OAacq and SMC conditions in regions of interest placed at the peak coordinates for frontal foci in Table 2. Only the pre-SMA demonstrated a significant correlation with task performance. Specifically, the change in rCBF in the pre-SMA demonstrated a significant inverse correlation with both trials to the criterion ($r = -.80$, $p < .01$) and to the number of incorrect responses ($r = -.84$, $p < .005$), indicating that greater activity in the pre-SMA was associated with more rapid task acquisition (see Figure 4).

There exists an interpretational drawback in the contrast between the OAacq and SMC conditions, in that it is unclear whether regions were activated in association with the trial-and-error acquisition of the task rules or with the actual performance of OA. To isolate areas that were specific to task acquisition, we contrasted the OAacq with the OApract conditions. Table 3 displays the results of this contrast. The left pre-SMA again emerged as the highest magnitude focus in this contrast, indicating that this response is relatively specific to acquiring the OA task rather than

Table 2
*OA Acquisition: Sensorimotor Control in Subjects Reaching Criterion Performance (n = 6)*

| Area | Coordinates | $z$ score |
|---|---|---|
| Frontal lobe | | |
| Left pre-SMA (BA 6) | −6, 12, 47 | 4.4 |
| Left superior–lateral frontal pole (middle frontal gyrus; BA 10) | −48, 50, 9 | 3.6 |
| Left inferior frontal pole (frontomarginal gyrus; BA 10) | −6, 53, −16 | 3.4 |
| Right inferior frontal gyrus (pars orbitalis; BA 47/12) | 30, 41, −4 | 3.4 |
| Posterior regions | | |
| Right middle temporal gyrus (BA 21) | 57, −33, −4 | 3.7 |
| Left parietal–occipital transition zone (BA 19) | −24, −76, 36 | 3.3 |

*Note.* Talairach stereotactic coordinates in millimeters: $x$ = medial–lateral relative to midline (+ = right hemisphere); $y$ = anterior–posterior relative to the anterior commissure (+ = anterior); $z$ = inferior–superior relative to intercommissural plane (+ = superior). Peak areas of activation had $z$ scores above 3.3 and exceeded a threshold of $p = .0005$. OA = object alternation; pre-SMA = presupplemental motor area; BA = Brodmann area.

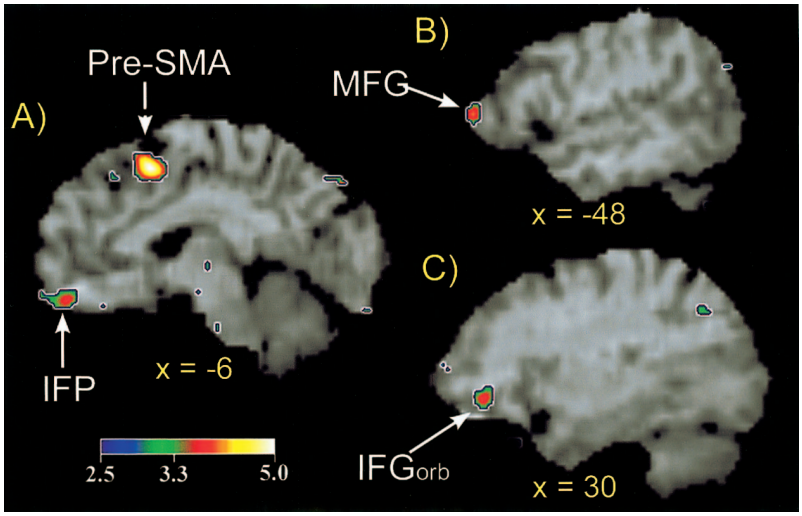


*Figure 3.* Activation during the object alternation acquisition condition relative to the sensorimotor control condition in subjects who acquired the task rule ($n = 6$). A: Presupplemental motor area (pre-SMA) and inferior frontal pole (IFP). B: Dorsal frontal pole in the anterior middle frontal gyrus (MFG). C: Inferior frontal gyrus, pars orbitalis ($IFG_{orb}$).

being a more general correlate of OA performance (see Figure 5). Similarly, responses again localized to the inferior frontal pole along the frontomarginal gyrus, with the right hemisphere focus reaching statistical significance, whereas the response in the left hemisphere just failed to reach statistical significance ($x = -12$, $y = 53$, $z = -16$; $z$ score = 3.25, $p = .006$). No significant activations emerged in either the VLPFC or the more superior frontopolar regions in this contrast. Outside the frontal lobe, significant responses arose in the superior parietal lobule along the intraparietal sulcus, the precuneus, the ventral occipital cortex, and the cerebellum.

## Discussion

The results of this experiment support the involvement of frontal lobe regions during the acquisition of OA in humans but indicate that increased activity during acquisition involves additional frontal regions beyond the VLPFC–LOFC region. Specifically, the left pre-SMA showed robust activations, with the magnitude of activation correlating with task performance. This finding is striking in that this area has neither theoretically nor empirically been previously associated with OA tasks.

Several features are notable about the pre-SMA's potential role in a task such as OA acquisition. First, Elliott and Dolan (1998) reported activation in a similar region during hypothesis testing regarding a task rule relative to simple guessing (they labeled this activation cingulate, but its location appears highly similar to that occurring in the present study). The OAacq condition clearly resembles the task used by Elliott and Dolan, in that subjects had to test hypotheses to acquire the task rule.

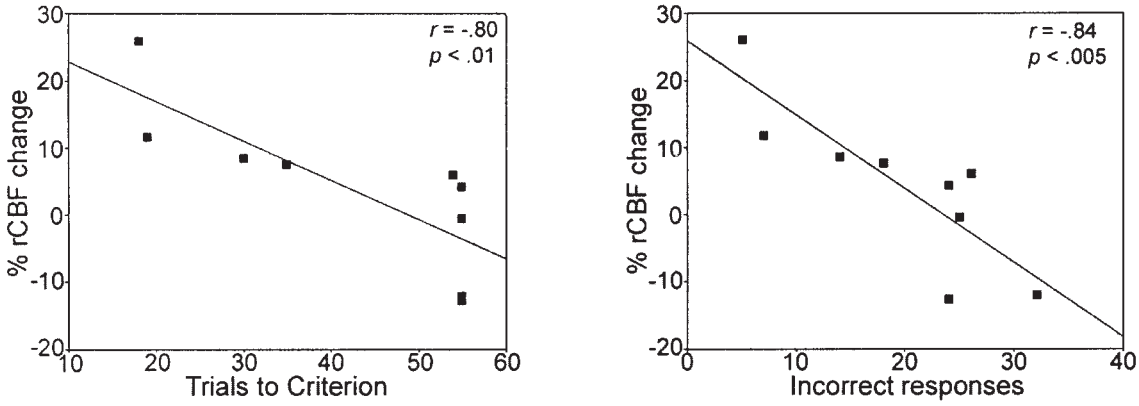


*Figure 4.* Scatter plots showing the correlation between change in the regional cerebral blood flow (rCBF) in the presupplemental motor area (between the object alternation acquisition and sensorimotor control conditions) and task performance, illustrated by trials to criterion and incorrect responses, during object alternation acquisition.

Table 3
*OA Acquisition: OA Practiced Performance in Subjects Reaching Criterion Performance (n = 6)*

| Area | Coordinates | z score |
|---|---|---|
| Frontal lobe | | |
| Left pre-SMA (BA 6) | −6, 14, 50 | 4.3 |
| Right inferior frontal pole (frontomarginal gyrus; BA 10) | 19, 57, −11 | 3.5 |
| Posterior regions | | |
| Right intraparietal sulcus (BA 7) | 28, −60, 38 | 5.0 |
| Left ventral occipital cortex (BA 17) | −6, −82, −18 | 4.5 |
| Right precuneus (BA 7) | 8, −51, 43 | 3.5 |
| Left superior parietal lobule (BA 7) | −24, −62, 45 | 3.5 |
| Right precuneus (BA 7) | 6, −64, 40 | 3.5 |
| Cerebellum (lobule VII) | 8, −73, −29 | 3.4 |

*Note.* Talairach stereotactic coordinates in millimeters: $x$ = medial–lateral relative to midline (+ = right hemisphere); $y$ = anterior–posterior relative to the anterior commissure (+ = anterior); $z$ = inferior–superior relative to intercommissural plane (+ = superior). Peak areas of activation had $z$ scores above 3.3 and exceeded a threshold of $p = .0005$. OA = object alternation; pre-SMA = presupplemental motor area; BA = Brodmann area.

Second, the pre-SMA (and the adjacent superior aspects of the anterior cingulate) has been argued to be critical in situations with high response conflict (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Carter et al., 1998; Garavan, Ross, Kaufman, & Stein, 2003; Garavan, Ross, Murphy, Roche, & Stein, 2002; Ullsperger & von Cramon, 2001, 2003). The present data are consistent with such a hypothesis, given the obviously greater level of conflict during OAacq, when the subject does not yet know the task rule relative to performance in the other conditions.

Deficits in OA acquisition have often been interpreted as reflecting a general problem with perseveration, in which subjects have difficulty inhibiting prepotent responses or prepotent response strategies (Bardenhagen & Bowden, 1998; Freedman et al., 1998; Mishkin, 1964; Mishkin & Manning, 1978). We find it of interest that both electrophysiological and neuroimaging studies point to the importance of the pre-SMA in tasks involving conflict between prepotent and less potent responses (Curtis & D'Esposito, 2003; Ikeda et al., 1999; Menon, Adleman, White, Glover, & Reiss, 2001; Mostofsky et al., 2003). Likewise, the pre-SMA becomes active during tasks involving attentional shifts, in which subjects must switch their responses from previously established (currently prepotent) task demands to new task demands (Nagahama et al., 1998, 1999). Thus, the ability to inhibit prepotent responses, which has been used to explain the ventral prefrontal cortices' role in acquiring alternation tasks, seems just as apt for describing the functions of the pre-SMA, especially in situations in which conflict occurs between the prepotent response and an alternative response. In the context of OA learning, subjects who are rapidly and robustly able to suppress prepotent strategies or responses in the face of error may possess a substantial advantage over subjects who fail to engage these processes.

Activations also emerged elsewhere in the frontal lobe during OAacq. The most striking of these emerged in the VLPFC ($IFG_{orb}$), arising in both the initial analysis and again in the more restricted analysis of subjects who reached the performance criterion. This finding is highly consistent with animal data indicating that lesions of the homologous regions in monkeys produce deficits in OA acquisition. However, on the basis of the present data, we suggest that activity in the region is not specifically related to task acquisition, in that the area did not remain significant in the contrast between OAacq and OApract. Moreover, activity in the area showed no association with successful task performance.

If VLPFC activity is not specific to task acquisition, what role might it play in the OA tasks? Although not formally tested by this study, it is quite possible that the VLPFC comes into play primarily with respect to its involvement in updating and maintaining representations in working memory (Fletcher & Henson, 2001; Owen, 2000). Such functions would be critical for both task

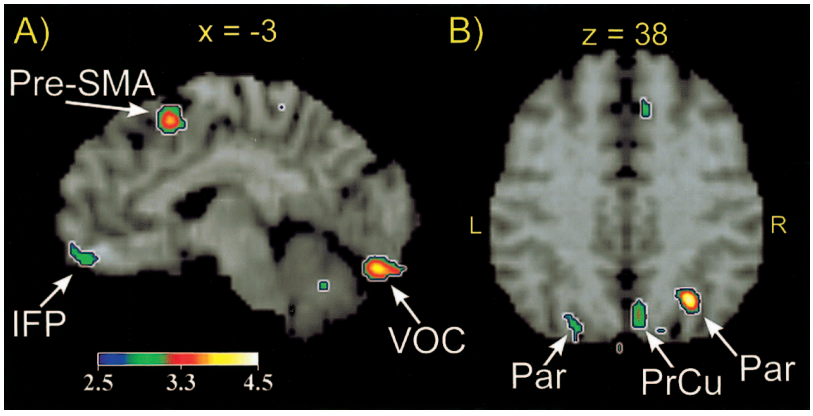


*Figure 5.* Activations during the object alternation acquisition condition relative to the practiced object alternation condition. A: Presupplemental motor area (pre-SMA) and the inferior frontal pole (IFP). Note that the area of the IFP shown just failed to reach statistical significance in this contrast ($p = .0006$), but an area in the left IFP does reach statistical significance. The peak of the pre-SMA focus is 3 mm lateral to this sagittal slice. VOC = ventral occipital cortex. B: Posterior activations, including bilateral parietal foci (Par) and the precuneus (PrCu). Note that the peak of the left parietal focus lies 7 mm superior to this slice, and the peak of both precuneus foci (only one of which is shown here) also localize to more superior slices.

acquisition and task performance. In the present study, even subjects who were unsuccessful at acquiring the task rule were likely to have engaged working memory mechanisms in trying to understand the task. Indeed, working memory is likely a necessary component for both task acquisition and practiced performance.

In contrast to the VLPFC, activations in the inferior frontal pole reached statistical significance in contrasts with both SMC and OApract conditions. Although the magnitude of the activation was not related to the speed of task acquisition, its emergence in contrasts with OApract nevertheless suggests that it was relatively specific to processes involved in acquiring the task. The inferior frontal pole remains poorly understood, and the area's poor signal quality in most fMRI studies does not help matters. Nevertheless, a similar region has been observed during rule learning (Berman et al., 1995; Nagahama et al., 1996; Strange et al., 2001) and during receipt of abstract rewards and punishments (O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001). Therefore, it may play a role in monitoring or responding to feedback during this type of trial-and-error learning task, especially when the feedback is critical to testing hypotheses about task rules.

In addition to the inferior frontal pole, a portion of the left superior frontal pole was also activated in the contrast of OAacq and SMC among subjects who correctly solved the task. Discussions of frontopolar cortex have rarely attempted to distinguish between processes supported by the superior versus the inferior frontal pole. Indeed, several examples exist in which activity emerged in both inferior and superior aspects of the frontal pole in the same task (Berman et al., 1995; Gold et al., 1996; Nagahama et al., 1996). However, the two areas showed at least a partial dissociation in the contrast with the OApract condition (with the inferior regions remaining more activated, whereas the superior regions did not). Other data on the effects of feedback, response selection, attentional shifts, and guessing and planning have also suggested the presence of inferior–superior frontopolar dissociations (Christoff & Gabrieli, 2000; Elliott & Dolan, 1998; Elliott, Frith, & Dolan, 1997; Pollmann, Weidner, Müller, & von Cramon, 2000), although a clear functional parcellation remains elusive.

In considering a possible role for the inferior frontopolar cortex in OAacq, it is worth noting that in animal and human lesion studies, this area was usually compromised in the course of ventrolateral lesioning. The clearest exception comes from a study by Mishkin and Manning (1978), in which deficient performance was seen in animals with lesions that were clearly limited to the VLPFC (although these lesions may have damaged fibers of passage). Most of the human frontal lobe patients with OA acquisition deficits reported by Freedman et al. (1998) possessed damage to the inferior frontal pole. The one exception was a patient with large anterior medial frontal lesions that included the inferior frontal pole, who demonstrated normal range acquisition. Thus, although the inferior frontal pole could contribute to some of the effects of ventral prefrontal lesions on OA performance, lesions of the area are probably not necessary to produce OA deficits (at least when these lesions occur in isolation).

Although the present study supports the involvement of the VLPFC and some additional frontopolar regions in OAacq, the strong activation of the pre-SMA and its correlation with successful task performance leads us to suggest caution in specifically attributing deficits in the acquisition of alternation tasks to VLPFC or OFC dysfunction. Indeed, if we base our conclusions on the size of activations, we need to consider the possibility that the pre-SMA may be as important, if not more important, in the acquisition of OA tasks. Of course, activation during a neuroimaging study does not necessarily mean that a region is required for the normal performance or acquisition of a task. Unfortunately, we know of no studies in which researchers have specifically examined the effects of pre-SMA lesions on OA acquisition in either humans or monkeys. However, an interesting parallel may exist to a recent study of the Wisconsin Card Sorting Test (WCST; Heaton, 1981) performance in patients with frontal lobe lesions. The WCST, which like OA acquisition requires trial-and-error learning and the ability to suppress prepotent incorrect strategies, has long been associated with DLPFC functioning (Milner, 1963). However, Stuss et al. (2000) indicated that patients with superior medial frontal lesions are also severely impaired on the WCST. At least in patients with large lesions of the superior medial frontal region, this deficit appears as severe as those produced by DLPFC lesions. Unfortunately, little information is available regarding patients with more restricted pre-SMA lesions—and it is possible that the underlying cingulate regions play a role in this deficit. Nevertheless, such data suggest that the pre-SMA may play a critical role in tasks previously thought to be more specifically associated with more lateral or ventral prefrontal regions.

To date, discussion of the neural substrates of OA acquisition and performance has rarely considered issues of lateralization. Most animal and human studies have involved subjects with bilateral lesions. Overall, no general pattern of hemispheric asymmetry has emerged from PET studies of OA (Curtis et al., 2000; Zald et al., 2002). Nevertheless, many of the activations are suggestive of regionally specific asymmetries. Although the interpretation of these asymmetries remains unclear, a full understanding of the neural substrates of OA in humans may require attention to this issue.

At present, there remain few neuropsychological probes that specifically tap the functions of the inferior frontal cortex. The strength of the OA task as a neuropsychological probe for this region lies in its long-established use in monkey lesion studies, the presence of a small amount of literature suggesting similar (if weaker) deficits in humans following inferior frontal lesions, and the observation of deficits in OA acquisition in numerous psychiatric and neurological patient groups. However, as with many clinical and experimental frontal lobe tasks, the ability to acquire OA is likely multidetermined, requiring several discrete cognitive processes that involve distributed networks of brain regions. The present data appear to support such an assertion, suggesting that several regions beyond the VLPFC–LOFC are probably critical for OA acquisition.

## References

Abbruzzese, M., Bellodi, L., Ferri, S., & Scarone, S. (1995). Frontal-lobe dysfunction in schizophrenia and obsessive–compulsive disorder: A neuropsychological study. *Brain and Cognition, 27,* 202–212.

Abbruzzese, M., Ferri, S., & Scarone, S. (1997). The selective breakdown of frontal functions in patients with obsessive–compulsive disorder and in patients with schizophrenia: A double dissociation experimental finding. *Neuropsychologia, 35,* 907–912.

Bardenhagen, F. J., & Bowden, S. C. (1998). Cognitive components in perseverative and nonperseverative errors on the object alternation task. *Brain and Cognition, 37,* 224–236.

Berman, K. F., Ostrem, J. L., Randolph, C., Gold, J., Goldberg, T. E., Coppola, R., et al. (1995). Physiological activation of a cortical network during performance of the Wisconsin Card Sorting Test: A positron emission tomography study. *Neuropsychologia, 33,* 1027–1046.

Botvinick, M. M., Braver, T. S., Barch, D. M., Carter, C. S., & Cohen, J. D. (2001). Conflict monitoring and cognitive control. *Psychological Review, 108,* 624–652.

Carter, C. S., Braver, T. S., Barch, D. M., Botvinick, M. M., Noll, D., & Cohen, J. D. (1998, May 1). Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science, 280,* 747–749.

Cavedini, P., Ferri, S., Scarone, S., & Bellodi, L. (1998). Frontal lobe dysfunction in obsessive–compulsive disorder and major depression: A clinical-neuropsychological study. *Psychiatry Research, 78,* 21–28.

Christoff, K., & Gabrieli, J. D. (2000). The frontopolar cortex and human cognition: Evidence for a rostrocaudal hierarchical organization within the human prefrontal cortex. *Psychobiology, 28,* 168–186.

Curtis, C. E., & D'Esposito, M. (2003). Success and failure suppressing reflexive behavior. *Journal of Cognitive Neuroscience, 15,* 409–418.

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.

Elliott, R., & Dolan, R. J. (1998). Activation of different anterior cingulate foci in association with hypothesis testing and response selection. *NeuroImage, 8,* 17–29.

Elliott, R., Frith, C. D., & Dolan, R. J. (1997). Differential neural response to positive and negative feedback in planning and guessing tasks. *Neuropsychologia, 35,* 1395–1404.

Faraone, S. V., Seidman, L. J., Kremen, W. S., Toomey, R., Pepple, J. R., & Tsuang, M. T. (1999). Neuropsychological functioning among the nonpsychotic relatives of schizophrenic patients: A 4-year follow-up study. *Journal of Abnormal Psychology, 108,* 176–181.

Fletcher, P. C., & Henson, R. N. (2001). Frontal lobes and human memory: Insights from functional neuroimaging. *Brain, 124,* 849–881.

Freedman, M. (1990). Object alternation and orbitofrontal system dysfunction in Alzheimer's and Parkinson's disease. *Brain and 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.

Gansler, D. A., Covall, S., McGrath, N., & Oscar-Berman, M. (1996). Measures of prefrontal dysfunction after closed head injury. *Brain and Cognition, 30,* 194–204.

Garavan, H., Ross, T. J., Kaufman, J., & Stein, E. A. (2003). A midline dissociation between error-processing and response-conflict monitoring. *NeuroImage, 20,* 1132–1139.

Garavan, H., Ross, T. J., Murphy, K., Roche, R. A. P., & Stein, E. A. (2002). Dissociable executive functions in the dynamic control of behavior: Inhibition, error detection, and correction. *NeuroImage, 17,* 1820–1829.

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

Goel, V., Gold, B., Kapur, S., & Houle, S. (1997). The seats of reason? An imaging study of deductive and inductive reasoning. *Neuroreport, 8,* 1305–1310.

Goel, V., Gold, B., Kapur, S., & Houle, S. (1998). Neuroanatomical correlates of human reasoning. *Journal of Cognitive Neuroscience, 10,* 293–302.

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.

Good, K. P., Kiss, I., Buiteman, C., Woodley, H., Rui, Q., Whitehorn, D., et al. (2002). Improvement in cognitive functioning in patients with first-episode psychosis during treatment with quetiapine: An interim analysis. *British Journal of Psychiatry, 181*(Suppl. 43), s45–s49.

Heaton, R. K. (1981). *A manual for the Wisconsin Card Sorting Test.* Odessa, FL: Psychological Assessment Resources.

Ikeda, A., Yazawa, S., Kunieda, T., Ohara, S., Terada, K., Mikuni, N., et al. (1999). Cognitive motor control in human pre-supplementary motor area studied by subdural recording of discrimination/selection-related potentials. *Brain, 122,* 915–931.

Knauff, M., Mulack, T., Kassubek, J., Salih, H. R., & Greenlee, M. W. (2002). Spatial imagery in deductive reasoning: A functional MRI study. *Brain Research: Cognitive Brain Research, 13,* 203–212.

Koenen, K. C., Driver, K. L., Oscar-Berman, M., Wolfe, J., Folsom, S., Huang, M. T., & Schlesinger L. (2001). Measures of prefrontal system dysfunction in posttraumatic stress disorder. *Brain and Cognition, 45,* 64–78.

Marie, R. M., Barre, L., Dupuy, B., Viader, F., Defer, G., & Baron, J. C. (1999). Relationships between striatal dopamine denervation and frontal executive tests in Parkinson's disease. *Neuroscience Letters, 260,* 77–80.

Mazoyer, B., Trebossen, R., Deutch, R., Casey, M., & Blohm, K. (1991). Physical characteristics of the ECAT 953B/31: A new high resolution brain positron tomograph. *IEEE Transactions in Medical Imaging, 10,* 499–504.

Menon, V., Adleman, N. E., White, C. D., Glover, G. H., & Reiss, A. L. (2001). Error-related brain activation during a go/nogo response inhibition task. *Human Brain Mapping, 12,* 131–143.

Milner, B. (1963). Effects of different brain lesions on card sorting. *Archives of Neurology, 9,* 90–100.

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., et al. (1993). Automated detection of the intercommissural line for stereotactic localization of functional brain images. *Journal of Nuclear Medicine, 34,* 322–329.

Mishkin, 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.

Mostofsky, S. H., Schafer, J. G., Abrams, M. T., Goldberg, M. C., Flower, A. A., Boyce, A., et al. (2003). fMRI evidence that the neural basis of response inhibition is task-dependent. *Brain Research: Cognitive Brain Research, 17,* 419–430.

Nagahama, Y., Fukuyama, H., Yamauchi, H., Matsuzaki, S., Konishi, J., Shibasaki, H., et al. (1996). Cerebral activation during performance of a card sorting test. *Brain, 119,* 1667–1675.

Nagahama, Y., Okada, T., Katsumi, Y., Hayashi, T., Yamauchi, H., Sawamoto, N., et al. (1999). Transient neural activity in the medial superior frontal gyrus and precuneus time locked with attention shift between object features. *NeuroImage, 10,* 193–199.

Nagahama, Y., Sadato, N., Yamauchi, H., Katsumi, Y., Hayashi, T., Fukuyama, H., et al. (1998). Neural activity during attention shifts between object features. *Neuroreport, 9,* 2633–2638.

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.

Öngür, D., Ferry, A. T., & Price, J. L. (2003). Architectonic subdivision of the human orbital and medial prefrontal cortex. *Journal of Comparative Neurology, 460,* 425–449.

Oscar-Berman, M., & Bardenhagen, F. (1998). Nonhuman animal models of memory dysfunction in neurodegenerative disease. In A. Tröster (Ed.), *Memory in neurodegenerative disease* (pp. 3–20). New York: Cambridge University Press.

Owen, A. M. (2000). The role of the lateral frontal cortex in mnemonic processing: The contribution of functional neuroimaging. *Experimental Brain Research, 133,* 33–43.

Pantelis, C., & Brewer, W. (1995). Neuropsychological and olfactory dysfunction in schizophrenia: Relationship of frontal syndromes to syndromes of schizophrenia. *Schizophrenia Research, 17,* 35–45.

Parsons, L. M., & Osherson, D. (2001). New evidence for distinct right and left brain systems for deductive versus probabilistic reasoning. *Cerebral Cortex, 11,* 954–965.

Picard, N., & Strick, P. L. (1996). Motor areas of the medial wall: A review of their location and functional activation. *Cerebral Cortex, 6,* 342–353.

Pollman, S., Weidner, R., Müller, H. J., & von Cramon, D. Y. (2000). A fronto-posterior network involved in visual dimension changes. *Journal of Cognitive Neuroscience, 12,* 480–494.

Pribram, K. H., & Mishkin, M. (1956). Analysis of the effects of frontal lesions in monkey: III. Object alternation. *Journal of Comparative and Physiological Psychology, 49,* 41–45.

Robins, L. N., & Marcus, S. C. (1988). *Computer-administered Diagnostic Interview Schedule*. *Version I.* St. Louis, MO: Washington University.

Seidman, L. J., Oscar-Berman, M., Kalinowski, A. G., & Ajilore, O. (1995). Experimental and clinical neuropsychological measures of prefrontal dysfunction in schizophrenia. *Neuropsychologia, 9,* 481–490.

Strange, B. A., Henson, R. N., Friston, K. J., & Dolan, R. J. (2001). Anterior prefrontal cortex mediates rule learning in humans. *Cerebral Cortex, 11,* 1040–1046.

Stuss, D. T., Levine, B., Alexander, M. P., Hong, J., Palumbo, C., Hamer, L., et al. (2000). Wisconsin Card Sorting Test performance in patients with focal frontal and posterior brain damage: Effects of lesion location and test structure on separable cognitive processes. *Neuropsychologia, 38,* 388–402.

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

Ullsperger, M., & von Cramon, D. Y. (2001). Subprocesses of performance monitoring: A dissociation of error processing and response competition revealed by event-related fMRI and ERPs. *NeuroImage, 14,* 1387–1401.

Ullsperger, M., & von Cramon, D. Y. (2003). Error monitoring using external feedback: Specific roles of the habenular complex, the reward system, and the cingulate motor area revealed by functional magnetic resonance imaging. *Journal of Neuroscience, 23,* 4308–4314.

Worsley, K. J., Evans, A. C., Marrett, S., & Neelin, P. (1992). A 3-dimensional statistical analysis for cbf activation studies in human brain. *Journal of Cerebral Blood Flow and Metabolism, 12,* 900–918.

Zald, D. H., Curtis, C., Folley, B. S., & Pardo, J. V. (2002). Prefrontal contributions to delayed spatial and object alternation: A positron emission tomography study. *Neuropsychology, 16,* 182–189.

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.

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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