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Neuropsychologia 43 (2005) 1598–1608

NEUROPSYCHOLOGIA

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Brain activations associated with probability matching

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Received 17 June 2004; received in revised form 14 January 2005; accepted 19 January 2005
Available online 7 April 2005

Abstract

Previously, in a simple probability-matching experiment with two split-brain patients that involved having the participant predict which of two events will happen on the next trial, we found that the left hemisphere tended to look for patterns and match the frequency of previous occurrences but not the right hemisphere [Wolford, G., Miller, M. B., & Gazzaniga, M. S. (2000). The left hemisphere's role in hypothesis formation. *Journal of Neuroscience*, *20*(RC64), 1–4]. In this study, we examined those findings in normal subjects using fMRI. Subjects alternated between blocks of trials in which they predicted the location of a stimulus and those in which they detected the location of a stimulus. Previous investigators using similar paradigms reported mostly right hemisphere activations, including activations in the right dorsolateral and ventrolateral prefrontal cortex, the medial prefrontal cortex, and the right lateral parietal lobe. We also found mostly right hemisphere activations, but we found that some of the activations in the dorsolateral prefrontal and parietal cortices were sensitive to individual differences in the tendency to look for patterns in random sequences. Further, we found that, by controlling for the working memory component of the predicting task, all brain activations in the normal brain associated with looking for patterns were related to the task demands of working memory processes underlying probability matching and predicting.

Keywords: fMRI; Frequency matching; Decision-making; Prefrontal cortex

1. Introduction

Over the last three decades, Gazzaniga and colleagues have demonstrated that the left hemisphere of the human brain has a unique capacity and drive to interpret the world around it (Gazzaniga, 2000). One instantiation of this 'interpreter' is the tendency to formulate hypotheses about a sequence of events. In a world in which the sequence of events is often deterministic and causal, the human drive to formulate hypotheses about the sequence of events has adaptive value. But many sequences of events are random (e.g., the timing and location of raindrops on a sidewalk), and to base a decision on some hypothetical formulation of a random sequence can be nonoptimal. Recently, in a simple probability-matching paradigm that involves having the participant guess which of two events will happen on the next trial, we demonstrated the left hemisphere's need to look for patterns in a random sequence. Typically, humans' "frequency match", that is, they tend to predict the alternatives in the proportion to which they have been presented in the past. So, if the two alternatives are 'top' and 'bottom' and top occurs on 70% of the trials, participants predict 'top' about 70% of the time. Frequency matching is curious because the optimal strategy is to maximize, that is, to always choose the most frequent alternative. Species other than humans consistently maximize (Hinson & Staddon, 1983). We found that the left hemisphere of split-brain patients frequency matches, but that the right hemisphere maximizes (Wolford, Miller, & Gazzaniga, 2000).

In this study, we examined this finding with normal subjects using fMRI. Subjects alternated between blocks in which they predicted the occurrence of a stimulus (in 70% of the trials, the stimulus occurred at the top of the screen)

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0028-3932/$ – see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.neuropsychologia.2005.01.021

and blocks in which they detected the location of a presented stimulus. Interestingly, other investigators using similar paradigms to investigate the neural substrates of guessing and predicting have reported activations predominantly in the right hemisphere and not the left (Elliott & Dolan, 1998; Elliott, Rees, & Dolan, 1999; Huettel, Mack, & McCarthy, 2002; Schubotz & von Cramon, 2002; Volz, Schubotz, & von Cramon, 2003). For example, Elliott et al. (1999) found activations in normal subjects in the right dorsolateral prefrontal cortex, bilateral inferior parietal lobe, right anterior cingulate, and right ventromedial orbitofrontal cortex associated with guessing either the suit or the color of a playing card.

In this study, we observed brain activity associated with looking for patterns in a probability-matching paradigm compared to simply detecting the location of a stimulus. A critical difference between our current "prediction" study and the "guessing" studies conducted by others (Elliott et al., 1999; Paulus et al., 2001) is that we set the probability of one alternative to occur more frequently than the other alternative (or alternatives). With equally probable stimuli, it is difficult to detect strategic behavior on the part of the subjects. For example, Elliott and colleagues determined that the subjects were engaged in strategically looking for patterns based on verbal queries of some of the subjects afterwards. However, in a probability-matching paradigm, like the one we employed, strategic behavior can be observed in their choices. This allows us to distinguish subjects who are using different strategies. If brain activations are dependent on strategies, then the pattern of brain activity should be quite different for subjects who maximize versus those who search for patterns.

Based on our previous study with split-brain patients, we predicted mostly left hemisphere activations associated with pattern seeking. However, as mentioned above, other investigators using a similar prediction task as ours found predominantly right hemisphere activations. For example, subjects in the Volz et al. (2003) study produced a similar pattern of activation as others while predicting events with varying probabilities. Although the focus of their study was on the frontomedial activations associated with the predicting task, the preponderance of activations was again lateralized to the right hemisphere. These findings are at odds with our studies on split-brain patients. However, much of the activity in the right hemisphere could be attributed to the working memory component of the prediction task. We postulate that the formulation of a hypothesis necessarily involves a working memory component, though hypothesis formation also depends on other processes beyond working memory. As for engaging a working memory component, if subjects were explicitly looking for a pattern in a sequence of events in order to make a prediction, then they must keep track of the most recent sequence of trials in order to formulate that hypothesis. It is known that *n*-back working memory tasks using spatial locations as the stimuli produce mostly right hemisphere activations very similar to the pattern of activations reported in these prediction and guessing studies (D'Esposito et al., 1998). Although other investigators have suggested that working memory may be contributing to the activations associated with guessing or predicting (Elliott et al., 1999), no neuroimaging study, that we know of, attempted to control the working memory component of the contrasting task.

Previously, we have shown that a concurrent 3-back working memory task will move subjects from a frequency-matching strategy in a prediction task to a maximizing strategy (Wolford, Newman, Miller, & Wig, 2004), suggesting that working memory is a critical component of forming a hypothesis and making a prediction. If brain activations associated with predicting are due to the working memory component of the task, then varying the working memory load should significantly affect the activations. Since we are depending on the contrast between predicting and detecting in our task, we could take two different approaches to this manipulation. One, we could directly vary the load of the prediction task, but it is not clear to us how to accomplish this. Or, two, we could vary the load of the contrasting detection task. So in this study, we compared subjects' activations when contrasting predicting to detecting stimuli that just occurred to the same subjects' activations when contrasting predicting to detecting stimuli that occurred three trials back. As we have shown before, a 3-back working memory task is sufficiently difficult to interfere with frequency matching, so its use as a contrasting task should cancel any activation due to the working memory component of the prediction task.

We had three goals in this study: (1) to determine a pattern of activations in the normal brain that is associated with looking for patterns and to determine whether these regions are sensitive to individual differences in the tendency to look for patterns in random sequences; (2) to explicitly test the laterality of the pattern of activations given that our previous study with split-brain patients indicated a left hemisphere process while previous neuroimaging studies indicated a right hemisphere process; (3) to determine the extent to which brain activations in the normal brain associated with looking for patterns can be attributed to the task demands of a working memory component.

2. Methods

2.1. Subjects

Twenty-two right-handed subjects (10 males), aged between 18 and 44 years, volunteered for the experiment. Subjects were paid US$ 20 per session. Subjects were medically screened prior to scanning, and any subject with a neurological history or pregnancy at the time of scanning was excluded. All functional magnetic resonance imaging was conducted at the Dartmouth Brain Imaging Center. The use of human participants and fMRI procedures followed a protocol approved by The Committee for the Protection of Human Participants at Dartmouth College.

Table 1
Individual subject performance on the prediction task

Subject	Scan 1	Scan 2	Behavior	% "top"
01	Predict vs. Detect 1-back	Predict vs. Detect 1-back	FM	64
02	Predict vs. Detect 1-back	Predict vs. Detect 1-back	FM	56
03	Predict vs. Detect 1-back	Predict vs. Detect 1-back	FM	79
04	Predict vs. Detect 1-back	Predict vs. Detect 1-back	FM	71
05	Predict vs. Detect 1-back	Predict vs. Detect 1-back	FM	77
06	Predict vs. Detect 1-back	Predict vs. Detect 1-back	FM	66
07	Predict vs. Detect 1-back	Predict vs. Detect 1-back	Max	97
08	Predict vs. Detect 1-back	Predict vs. Detect 1-back	FM	67
09	Predict vs. Detect 1-back	Predict vs. Detect 1-back	FM	67
10	Predict vs. Detect 1-back	Predict vs. Detect 3-*back*	FM	66
12	Predict vs. Detect 1-back	Predict vs. Detect 3-*back*	FM	64
14	Predict vs. Detect 1-back	Predict vs. Detect 3-*back*	FM	66
16	Predict vs. Detect 1-back	Predict vs. Detect 3-*back*	Max	93
18	Predict vs. Detect 1-back	Predict vs. Detect 3-*back*	Max	92
20	Predict vs. Detect 1-back	Predict vs. Detect 3-*back*	FM	79
22	Predict vs. Detect 1-back	Predict vs. Detect 3-*back*	FM	82
11	Predict vs. Detect 3-*back*	Predict vs. Detect 1-back	FM	74
13	Predict vs. Detect 3-*back*	Predict vs. Detect 1-back	FM	67
15	Predict vs. Detect 3-*back*	Predict vs. Detect 1-back	FM	62
17	Predict vs. Detect 3-*back*	Predict vs. Detect 1-back	FM	70
19	Predict vs. Detect 3-*back*	Predict vs. Detect 1-back	Max	95
21	Predict vs. Detect 3-*back*	Predict vs. Detect 1-back	FM	66

FM: frequency matcher; Max: maximizer; % "top": the overall proportion that the most frequent stimulus was chosen across all 10 blocks of the prediction task.

2.2. Behavioral paradigm

The scanning session included two functional imaging scans. Each scan included either alternating blocks of a predict condition and a detect 1-back condition or alternating blocks of a predict condition and a detect 3-back condition. As shown in Table 1, subjects were divided into three groups. The groups varied according to whether and when they participated in the scan with the detect 3-back condition.

The scan which included detect 1-back trials consisted of 10 alternating blocks of trials, 5 blocks of prediction trials and 5 blocks of detection trials. A prediction block of 40 trials was indicated when the word PREDICT was presented at the center of the computer screen for 2 s. This cue was followed by 40 trials. Each trial began with the word "predict?" displayed at the center of the screen for 1250 ms. During this time, subjects were instructed to indicate with a button press whether they thought a stimulus would appear at the top or the bottom of the computer screen. This was immediately followed by either a red square that would appear at the top of the screen or a green circle that would appear at the bottom of the screen for 250 ms. The stimuli were randomly presented, but for 70% of the prediction trials the stimulus appeared at the top location and for 30% of the trials the stimulus appeared at the bottom location. After the appearance of the stimulus, a crosshair was presented for 500 ms at the center of the screen. A detection block of 40 trials was indicated when the word DETECT was displayed at the beginning of the block for 2 s. Rather than subjects predicting what location they thought a stimulus would appear, the subjects in the detect trials simply indicated whether the previous occurrence of a stimulus had appeared in the top or bottom location. Specifically, a red square would appear at the top of the screen or a green circle would appear at the bottom of the screen (probability was set at 50% for either location) for 250 ms. This was immediately followed by the word "where?" presented at the center of the screen for 1250 ms. The subject then indicated with a button press whether the preceding stimulus appeared at the top or bottom location. The trial ended with a crosshair at the center of the screen for 500 ms. A 50% probability was used in the detection blocks instead of the 70% that was used in the prediction blocks because we found in pilot studies that if we matched the probability setting of the prediction blocks that subjects had a tendency to keep looking for patterns during the detection blocks as well. We believe that this method was worth using, despite the possible confound of using different probability levels.

The scan with the detect 3-back condition included a modification of the detection trials. Instead of detecting what stimulus had just occurred, the subjects were instructed to detect what stimulus had occurred three trials back. This required the subjects to always keep track of the last three trials during the detection blocks. As shown in Table 1, seven of the subjects participated in the scan with the 1-back detection blocks first, while six of the subjects participated in the scan with the 3-back detection blocks first. No activation differences occurred due to the order of the scans with the detect 3-back condition.

2.3. MRI imaging parameters

Scans were collected at the Dartmouth Brain Imaging Center using a 1.5 T GE SIGNA Echospeed MRI scanner (General Electric, Milwaukee, WI) equipped with high-performance gradients (revision LX 8.3, maximum amplitude 4.0 mT/m, slew rate 150 mT/(m s)). During each session a 27-slice, T1-weighted structural image was acquired for each subject in the same slice prescription as the functional scans (TR = 650 ms, TE = 6.6 ms, fast spin-echo pulse sequence, with an in-plane resolution of 192 pixel × 192 pixel in a FOV of 24 cm, producing voxels of 1.25 mm × 1.25 mm × 5 mm) and a high resolution, T1-weighted structural image was acquired as well using a 3-D SPGR pulse sequence (TR = 25 ms, TE = 6 ms, RF flip angle = 250°, bandwidth = 15.6 kHz, voxel size = .9375 mm × 1.25 mm × 1.2 mm). Each session also included two functional scans acquired with gradient-recalled echoplanar imaging (TR = 2000 ms, TE = 35 ms, RF flip angle = 90°, gradient-echo pulse sequence, 27 contiguous axial slices at 5 mm thick, and an in-plane resolution of 64 pixel × 64 pixel in an FOV of 24 cm, producing voxels of 3.75 mm × 3.75 mm × 5 mm) (Kwong et al., 1992; Ogawa et al., 1992). Foam padding was used for head stabilization.

2.4. fMRI data analysis

Data were analyzed using Statistical Parametric Mapping (SPM99b; Wellcome Department of Cognitive Neurology, London, UK) (Friston et al., 1995). Motion correction to the first functional scan was performed within each participant using a six-parameter rigidbody transformation. The 27-slice structural image was then co-registered to the high-resolution structural image, and the resulting transformation parameters were applied to the mean of the motion-corrected images and all motion-corrected functional images. Using mutual information co-registration, the functional images were then directly co-registered to the high-resolution structural image. Spatial normalization to the Montreal Neurological Institute template (Talairach & Tournoux, 1988) was performed by applying a 12-parameter affine transformation followed by a nonlinear warping using basis functions (Ashburner & Friston, 1999). All transformations were computed sequentially with one re-slice operation at the end, and the functional images were written with 3 mm × 3 mm × 3 mm voxels. The spatially normalized scans were smoothed with an 8-mm isotropic Gaussian kernel to accommodate anatomical differences across participants. These smoothed and normalized images were then used for statistical analysis.

For each subject, and for each voxel, simple *t*-contrasts were based on a general linear model that included covariates for each of the conditions within each functional run and a linear regressor to account for signal drift. A random-effects model was then used to make statistical inferences in a group analysis (Friston et al., 1999). The initial group analyses of 18 subjects were based on one-sample *t*-tests with a threshold for significance of $p < .05$ (corrected for multiple comparisons) and a minimum voxel extent of 10. The subsequent group analyses of 10 subjects used a more liberal threshold of $p < .01$ (uncorrected for multiple comparisons) because of the implications of a null effect on our hypothesis.

A region of interest analysis was performed at 3 mm × 3 mm × 3 mm voxel cubes around the local maxima of the key regions of interest. This analysis entailed computing the percent signal change between predict and detect epochs on a subject-by-subject basis. These ROIs were then used for further statistical analysis of individual differences and laterality.

3. Results

3.1. Behavioral results

Subjects who look for patterns in the sequence of trials in which the stimulus appears at the top will match the frequency of the occurrence of the "top" stimulus in their predictions (Wolford et al., 2000). We consider behavior maximizing when the subject chooses the most frequent stimulus in a proportion that is at least three standard deviations above frequency matching, which in this case would be above .84. Out of the 22 subjects tested, 18 of the subjects' frequency matched across the 10 blocks of trials (see Table 1 and Fig. 1C), i.e., they chose the "top" stimulus on approximately 70% of the trials (within 14%). None of these subjects maximized their predictions by the last block of trials. Four subjects maximized their predictions, i.e., after the first few blocks they chose only the most frequent stimulus. This, of course, was the most optimal decision. Interestingly, one of the maximizing subjects indicated to the experimenter that he knew he would get the most accurate responses if he just chose the "top" stimulus on all the trials. All subjects were 100% correct on the 1-back detection trials, while the 13 subjects that participated in the 3-back detection trials averaged 83% correct across those trials.

3.2. fMRI results: activations associated with looking for patterns

Group analysis included all 18 subjects that frequency matched (see Table 1). Fig. 1A and Table 2 display regions that were significantly more active during the predict blocks than during the detect blocks across the group of subjects. These activations included wide regions of the prefrontal cortex and the parietal lobe. Surprisingly, the most significant activations occurred in the right hemisphere. The prefrontal regions included the dorsolateral prefrontal cortex (middle frontal gyrus (Brodmann areas (BA) 9 and 6), the ventrolateral prefrontal cortex (inferior frontal gyrus (BA 47)), the anterior prefrontal cortex (superior frontal gyrus (BA 10)), and the medial prefrontal cortex (medial frontal gyrus (BA 6 and 9)). There was also a significant activation in the right

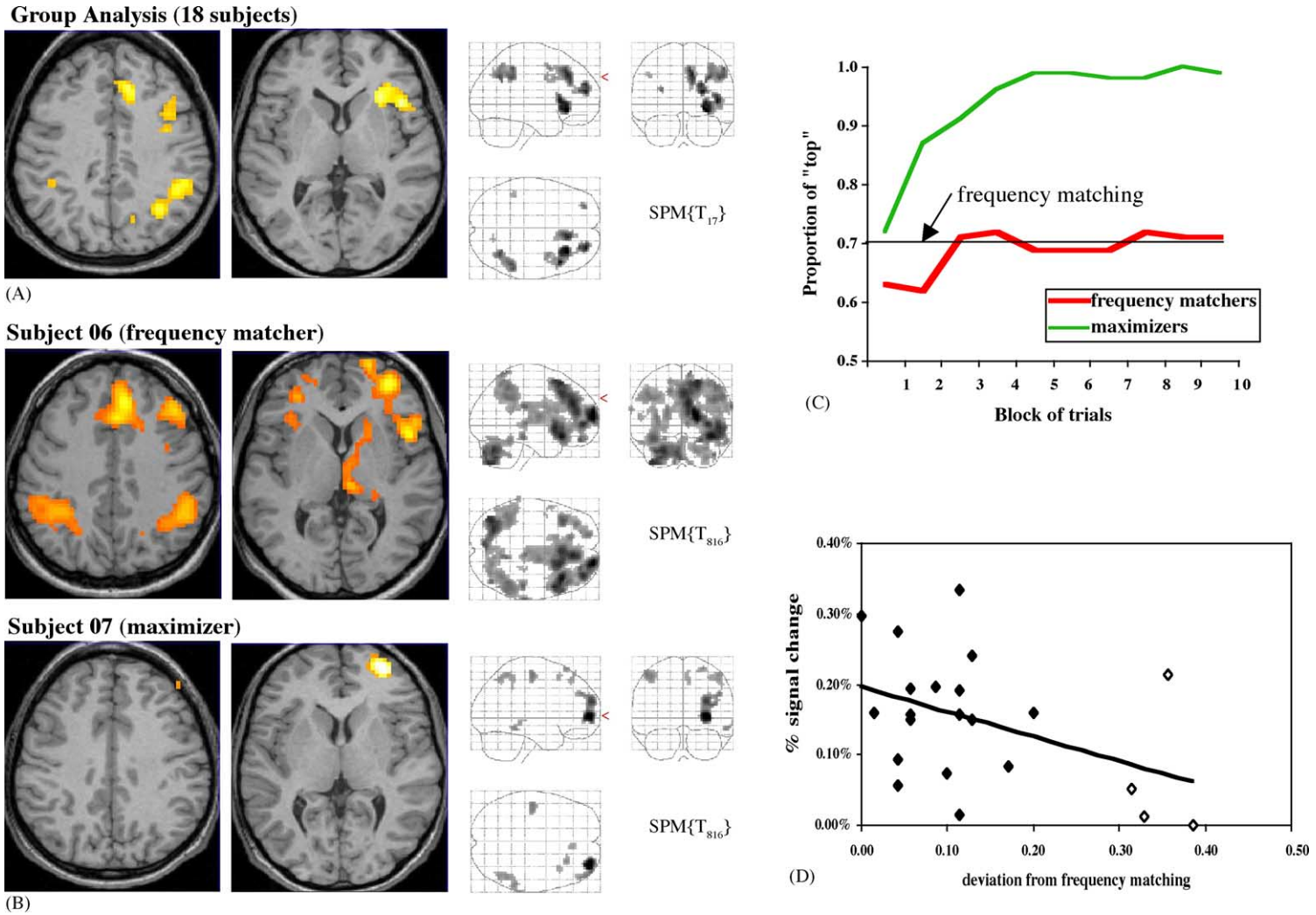

Fig. 1. (A) Axial slices ($z = 36$ and 3) and the glass brain from a group analysis (random effects; $p < .05$ corrected for multiple comparisons and a voxel extent of 10) of 18 subjects contrasting the predict condition with detect condition. (B) Same slice locations for two representative subjects ($p < .05$ corrected for multiple comparisons and a voxel extent of 10) for the same comparison. Subject #06 frequency matched on the predict trials, while Subject #07 maximized. (C) Behavioral results from the prediction task of the 22 subjects. Eighteen subjects frequency matched (i.e., they matched the probability of the most frequent stimulus), while four subjects maximized (i.e., always chose the most frequent stimulus). (D) The significant correlation between the mean percent signal change for the Predict vs. Detect contrast in the right middle frontal gyrus and the right angular gyrus and the deviation from frequency matching. The open symbols indicate the data points from the four maximizers.

Table 2
Regions based on peak activations of increased activity

Brain region	BA	*x*	*y*	*z*	*z*-Score	Extent
Predict vs. Detect 1-back ($n = 18$; $p < .05$ corrected)						
R. angular gyrus	39	33	−56	36	5.50	264
R. inferior frontal gyrus	47	45	20	2	5.84	231
R. medial frontal gyrus	6	12	31	34	5.78	174
R. superior frontal gyrus	10	27	53	14	5.85	105
R. middle frontal gyrus	9	42	13	32	4.93	54
R. middle frontal gyrus	6	36	5	47	5.01	20
L. superior frontal gyrus	10	−30	50	14	5.17	16
L. inferior frontal gyrus	40	−45	−39	38	4.76	14
R. precuneus	7	15	−65	39	4.81	12
Predict vs. Detect 3-back ($n = 10$; $p < .001$ uncorrected)						
L. posterior cingulate	30	−6	−58	6	3.44	84
L. precentral gyrus	4	−30	−24	54	3.50	68
R. lingual gyrus	19	9	−52	0	3.32	26
R. middle occipital gyrus	19	21	−87	10	3.41	18
L. superior temporal gyrus	13	−39	−23	7	2.93	10

BA: Brodmann area; *x*, *y*, and *z* are in Talairach coordinates; extent is in number of voxels.

angular gyrus (BA 39) that extended into the right inferior parietal lobule (BA 40). There was one small activation in the left superior frontal gyrus (BA 10) and in the left inferior parietal lobule (BA 40).

3.3. fMRI results: individual differences

There were observable differences in the pattern of activations between subjects that frequency matched and subjects that maximized. For example, Subject #06 (as shown in Fig. 1B) was a frequency matcher and produced a very similar pattern of activations as seen in the group analysis, while Subject #07 was a maximizer (the subject noted in the behavioral results) and produced none of the typical activations except a very discrete activation in the right anterior prefrontal cortex. However, there were not enough maximizing subjects (4) in our sample to produce meaningful group activation maps, and some maximizing subjects could still, conceivably, be looking for patterns and, therefore, produce similar patterns of activations as frequency matchers.

Nevertheless, we conducted a correlation between the percent signal change in key brain regions and the degree to which subjects deviated from frequency matching (see Table 1). Percent signal change between predict and detect conditions was collected for all 22 subjects in the first five brain regions listed in Table 2. This was correlated with a measure of the subjects' deviation for frequency matching, the absolute value of the ratio between the subject's actual proportion of "top" responses to the exact proportion of frequency matching (.70). Clearly, maximizers will have the largest deviations from frequency matching. We found that two regions (the right middle frontal gyrus and the right angular gyrus) showed strong negative correlations, that is, the more a subject deviated from frequency matching the lower the percent signal change in these regions. Fig. 1D shows the correlation between the mean percent signal change averaged across these two brain regions and the deviation from frequency matching ($r^2 = .184$, $F(1, 21) = 4.50$, $p < .047$). Three regions (the right inferior frontal gyrus, the right superior frontal gyrus, and the medial frontal gyrus) did not show a correlation between percent signal change and deviation from frequency matching. Clearly, these regions are more active during predict conditions than during detect conditions, but their activity is not modulated by individual differences in that deviation.

3.4. fMRI results: laterality

The group analysis of the 18 subjects that frequency matched indicate pattern of activations that were much stronger in the right hemisphere than in the left hemisphere, despite our hypothesis based on split-brain studies. We directly tested the laterality within the 18 subjects by comparing the mean percent signal change in four lateral regions of the right hemisphere to four homologous regions in the left hemisphere using a repeated measure ANOVA. The four ROIs in the right hemisphere were the same regions selected for the individual differences analysis. The percent signal change in the right hemisphere was significantly larger than the left hemisphere ($F(1, 17) = 29.887$, $p < .001$).

3.5. fMRI results: manipulating working memory load

Out of the 13 subjects from the two groups that included a scan with the detect 3-back condition, 10 of the subjects frequency matched during the predict blocks. Therefore, in these 10 subjects, we can compare within subjects the pattern of activations when comparing predict versus detect conditions to the pattern of activations when comparing predict versus detect 3-back conditions. The selection of a detect 3-back condition was not meant to be an equivalent task to the

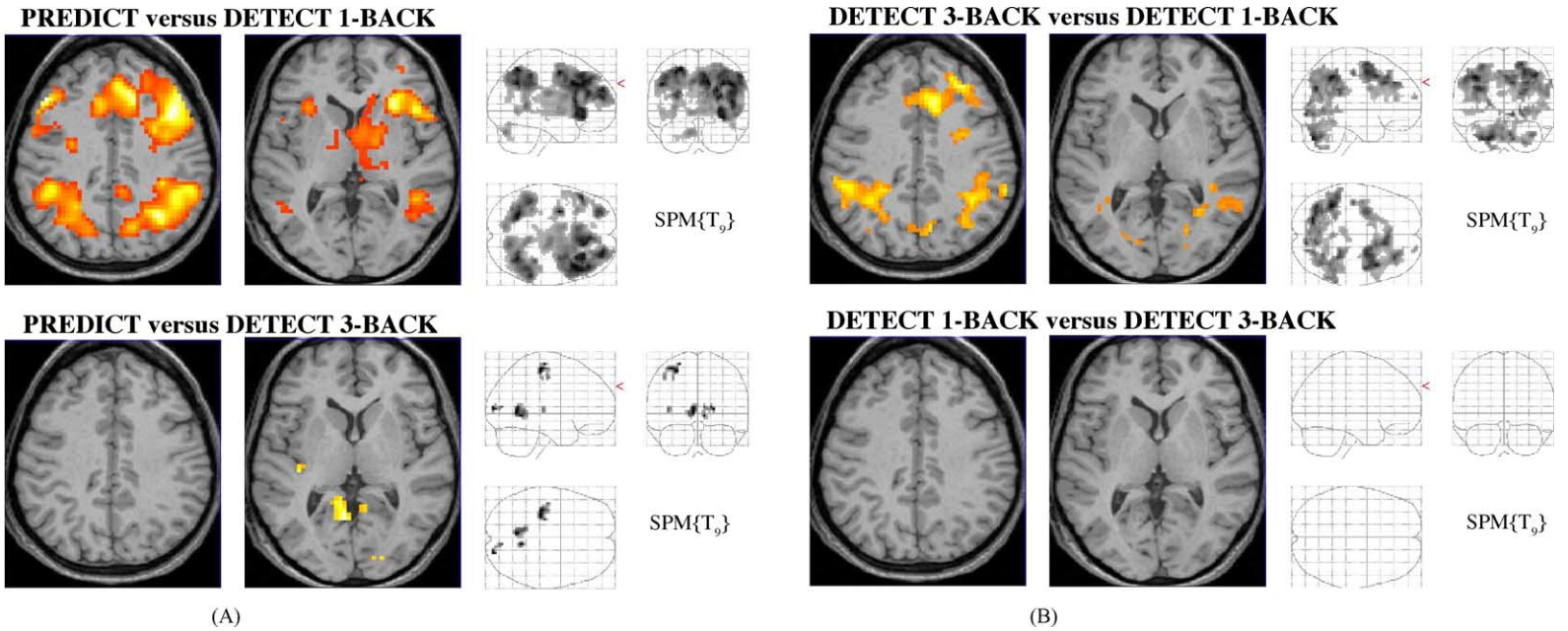

Fig. 2. (A) Axial slices ($z = 36$ and 3) and the glass brain from a group analysis (random effects; $p < .001$ uncorrected and a voxel extent of 10) of 10 subjects contrasting the predict condition with detect condition compared to the same slice locations in the same group of subjects contrasting the predict condition with detect 3-back condition. (B) Axial slices ($z = 36$ and 3) and the glass brain from a group analysis (random effects; $p < .001$ uncorrected and a voxel extent of 10) of 10 subjects contrasting the detect 3-back condition with detect condition compared to the same slice locations in the same group of subjects contrasting the detect condition with detect 3-back condition.

predict condition, but a sufficiently difficult task that should attenuate any signal of a contrasting task that depends on working memory processes.

Fig. 2A reveals the group analysis that was conducted on the 10 subjects that frequency matched. For the Predict versus Detect contrast, the pattern of activations are very similar to the earlier group analysis depicted in Fig. 1A, which was to be expected considering these 10 subjects are a subset of that group analysis. The pattern of activations is more extensive, though, given the lower statistical threshold ($p < .01$, uncorrected). Significant regions include the right and left dorsolateral prefrontal cortex (middle frontal gyrus (BA 9, 6, and 46)), the right and left ventrolateral prefrontal cortex (inferior frontal gyrus (BA 47)), the right and left anterior prefrontal cortex (superior frontal gyrus (BA 10)), the medial prefrontal cortex (BA 6), and the right and left parietal cortex (from the angular gyrus to the inferior parietal lobule (BA 39 and 40)). Again, the activations in the right hemisphere were stronger and more extensive than the activations in the left hemisphere.

During the Predict versus Detect 3-back contrast (Fig. 2A), all of the activations listed above were completely attenuated. None of the regions from the Predict versus Detect contrast showed up in the Predict versus Detect 3-back contrast, even at the more liberal threshold. This was further confirmed by masking the Predict versus Detect 3-back contrast with the Predict versus Detect contrast, and, again, no regions were significantly active. As shown in Fig. 2A and Table 2, there were some regions, though, that were significantly active during the Predict versus Detect 3-back contrast that were not significantly active during the Predict versus Detect contrast. One region, the precentral gyrus (BA 4), could be attributed to basic motor differences between predict and detect conditions, although it did not show up in the Predict versus Detect contrast. The other regions, the posterior cingulate (BA 30), the lingual gyrus (BA 19), and the left superior temporal gyrus (BA 13), could all be accounted for by resting state activity (Raichle et al., 2001). Distinct brain regions have been identified as more active during conditions of rest or less cognitive load than contrasting task conditions. If the detect 3-back condition was more difficult than the predict condition, then we would have expected some of these regions to be more active when making the Predict versus Detect 3-back contrast. Indeed, when we made the opposite comparison in the previous contrast, Detect versus Predict, we found that these same regions were more active. Excluding regions that can be accounted for by motor activity or resting state activity, no region was more active for the Predict versus Detect 3-back contrast.

Given that we had detect 3-back conditions and simple detect conditions within the same subjects, we conducted similar contrasts as with the predict conditions to see whether we would see similar patterns of activations. Indeed, we found similar activations, though less extensive, when comparing the detect 3-back condition to the detect condition (see Fig. 2B).

Our results clearly indicate that the patterns of activation attributed to predicting and looking for a pattern can be accounted for by the working memory component of the task.

4. Discussion

A common error in decision-making is to put forward a causal relationship when the evidence is inadequate or indicates a random relationship (Gilovich, Vallone, & Tversky, 1985; Kahneman & Tversky, 1973). We demonstrated this tendency by showing that most subjects frequency matched in a simple probability-matching paradigm. Previously, we have shown in split-brain studies that the left hemisphere tends to frequency match while the right hemisphere tends to maximize. We had three goals in this study. One goal was to determine the pattern of activations in the normal brain associated with looking for patterns and to determine whether these brain regions are sensitive to individual differences in frequency matching. The second goal was to test the laterality of these activations given the discrepancy between our split-brain studies and previous neuroimaging studies of predicting and guessing. The third goal was to determine the extent to which the pattern of activations attributed to predicting and looking for patterns could be accounted for by the working memory component of the task.

Looking for patterns and predicting the occurrence of a stimulus compared to simply detecting the occurrence of a stimulus produced a distinct pattern of activations that were mostly in the right hemisphere, including the right dorsolateral and ventrolateral prefrontal cortex, the right inferior and superior parietal lobule, and the right medial prefrontal cortex. This pattern of activation was quite consistent from subject to subject, which is an important consideration with higher order cognitive tasks (Miller et al., 2002). And, the patterns of activations that we report here are consistent with the sites of activations reported by others using similar "predicting" or "guessing" paradigms (Elliott & Dolan, 1998; Elliott et al., 1999; Huettel et al., 2002; Paulus et al., 2001; Schubotz & von Cramon, 2002; Volz et al., 2003).

Subjects consistently noted after the experiment that they were searching for a pattern in the sequence of locations despite its randomness. But there were also some notable exceptions in our sample to frequency matching. For example, one subject maximized and he had none of the activations noted above. He showed relatively little difference in brain activity between predicting and detecting the stimuli (except for a strong activation in the right anterior prefrontal cortex). He commented after the experiment that he realized early on that all he had to do was choose the most frequent stimulus on all the trials to get the most correct responses. Therefore, he had no need to search for patterns, and his pattern of brain activity may have reflected that behavior. Indeed, we found that activations in the right dorsolateral prefrontal and parietal cortices were significantly correlated with the degree to which subjects deviated from frequency matching (Fig. 1D).

Interestingly, fMRI studies of working memory have shown similar correlations between activations in these same regions and subject performance on working memory tasks (Rypma, Berger, & D'Espostio, 2002).

Our second goal was to assess the laterality of these activations given that our previous studies showed that frequency matching was a left hemisphere process based on split-brain studies. Yet, our results, which corroborate previous neuroimaging studies, clearly indicate mostly right hemisphere activity in the normal brain. How can these results with normal subjects in fMRI be reconciled with the results from split-brain patients and patients with unilateral prefrontal cortex damage? One possibility is that functioning in our relatively small number of patients is fundamentally different than functioning in normal subjects. In other words, if we had enough split-brain patients, we may find that more of them show frequency matching in the right hemisphere. Another possibility, is that the activations that we are seeing in the right hemisphere of normal brains is not due to predicting or looking for patterns per se, but to some other component process, such as working memory. This will be addressed in more detail further on.

If the activations in the right hemisphere of the normal brain are due to working memory processes, then it still leaves unresolved why we observe frequency matching only in the left hemisphere of split-brain patients? The split-brain results and the neuroimaging results, taken together, suggest a hierarchical prefrontal organization. Both hemispheres are capable of working memory functions, but in the intact brain spatial working memory preferentially engages the right hemisphere. However, the "interpreter" may reside exclusively in the left hemisphere. Therefore, in a disconnected brain, searching for patterns that involve working memory may only be realized in the hemisphere in which the "interpreter" resides. A similar dynamic between split-brain and neuroimaging results exists concerning episodic memory encoding (Wig, Miller, Kingstone, & Kelley, 2004).

Even if the right hemisphere activations can be satisfactorily attributed to the working memory component of the task, why are there no activations that can be attributed to predicting? One possible explanation is that the "interpreter", the proposed mechanism responsible for hypothesis formation and looking for patterns, is always turned on. A similar explanation has been used to explain why the hippocampus rarely shows differences in activation between memory conditions and non-memory conditions (Schacter & Wagner, 1999). Another possible explanation is that the interpreter is being shut off and on, but that our scanning procedure was not sensitive enough to detect the change. Indeed, one of the regions attributed to guessing and predicting in other studies is the ventromedial orbitofrontal cortex (Breiter, Aharon, Kahneman, & Dale, 2001; Critchley, Mathias, & Dolan, 2001; Elliott et al., 1999; O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001; Rogers et al., 1999). For example, Elliott et al. (1999) suggested that ventromedial orbitofrontal cortex mediates guessing while lateral prefrontal cortex mediates working memory associated with guessing. It is possible that we did not see this area active in our study because of the signal loss we observed in that general region due to sinus cavities. However, we did get good signal intensities in the location reported by Elliott et al. (Talairach coordinates: $x = 15$, $y = 27$, $z = -12$); the signal loss we observed occurred more medial and ventral to this area.

Is searching for a pattern predominantly a left hemisphere process? Our results of brain activity from normal subjects certainly do not provide further evidence for this claim. The notion that the interpreter is strictly a left hemisphere process based on split-brain studies is questionable given the lack of evidence from neuroimaging studies. Furthermore, more recent split-brain studies indicate that performance on a probability matching paradigm using faces instead of locations leads to frequency matching in the right hemisphere and not the left (Miller & Valsangkar-Smyth, in press), suggesting that the "interpreter" could be operating in both hemispheres depending on the type of stimuli. Yet, the opposite claim, that "predicting" and "guessing" are predominantly right hemisphere processes based on the neuroimaging studies, is also questionable based on our results that those activations can be completely attenuated by controlling for the working memory load. Future research will need to be conducted to determine whether activity can be linked specifically to the "interpreter" when working memory is accounted for.

A clear result from this fMRI study is that right hemisphere activations associated with predicting are the result of working memory processes in the service of the predicting task, rather than the result of necessarily searching for patterns. In order to find a pattern in a sequence of trials, it is necessary to keep track of the sequence and to continually update those locations in working memory. It is known that tasks involving spatial working memory activate regions of the lateral prefrontal cortex, medial prefrontal cortex, and lateral partial cortex (Courtney, Ungerleider, Keil, & Haxby, 1997; Gruber, Kleinschmidt, Binkofski, Steinmetz, & von Cramon, 2000; Leung, Gore, & Goldman-Rakic, 2002; Owen, Doyon, Petrides, & Evans, 1996; Petrides, Alivisatos, Evans, & Meyer, 1993), similar to the regions that we showed are associated with the predicting task. Indeed, Elliott et al. (1999) suggested that the pattern of activations (particularly those on the lateral surface) that they observed in their guessing task may be due to working memory processes. Yet, none of the predicting and guessing neuroimaging studies cited so far have attempted to directly control for working memory. In all of the previous studies, the contrasting task to predicting or guessing the occurrence of a stimulus was to detect or respond to what had just occurred; that is, the contrasting task had no working memory component to it.

In the current study, we included a condition in which the subjects had to detect the occurrence of a stimulus from three trials back. Previous studies have shown that increasing the level of difficulty on *n*-back tasks (even in dual task paradigms) will lead to incremental increases in BOLD

activations in the prefrontal cortex (Jaeggi et al., 2003). Previously, we have shown that a concurrent 3-back working memory task will move subjects from a frequency-matching strategy in a prediction task to a maximizing strategy (Wolford et al., 2004). In this study, we used a 3-back task as a contrasting condition, assuming that it was a difficult enough working memory load to attenuate any signal attributed to the contrasting prediction task that could actually be attributed to working memory. Indeed, what we found was that the right hemisphere activations that were evident when contrasting predicting to detecting-1-back trials were no longer evident in the same subjects when contrasting predicting to detecting-3-back trials, confirming that the original activations were due to the working memory component of the predicting task.

One region thought to be involved in "predicting" and "guessing" but distinct from working memory is the medial prefrontal cortex (Elliott et al., 1999; Volz et al., 2003). As noted earlier, the activation we report in the medial prefrontal cortex (BA 6) is more dorsal than the ventromedial orbitofrontal cortex reported by Elliott et al. (1999), but just slightly more ventral to the region (BA 8) reported by Volz et al. (2003). Volz et al. conducted a neuroimaging study with a prediction task in which the probability of the stimulus events varied across blocks of trials. They conducted a parametric analysis and found that activation of the mesial BA 8 increased significantly with increasing uncertainty (i.e., lower probability). However, its unknown how much working memory processes may have contributed to these activations. We found that significant activations in the medial frontal gyrus were completely attenuated by contrasting the prediction trials to detection trials that include a heavy working memory load. How regions of the medial prefrontal cortex respond to varying uncertainty versus varying cognitive load will be important in trying to understand the dynamics of this region and its contributions to decision making.

Hypothesis formation and searching for patterns is a critical factor in human decisions. Clearly, studies with split-brain patients and focal lesion patients suggest hemispheric differences in the performance of these tasks. Yet, fMRI results indicate a very different pattern of hemispheric involvement. Those patterns of activations, however, can be accounted for by working memory processes in support of the decision process. Reconciling the results from these two methods will be necessary for a complete understanding of the neural circuitry underlying frequency matching and pattern searching behavior that can lead to a more comprehensive understanding of various decision-making processes.

Acknowledgements

The authors would like to thank Barry Giesbrecht and Greg Ashby for comments on the manuscript and for their assistance in data analysis.

References

Ashburner, J., & Friston, K. J. (1999). Nonlinear spatial normalization using basis functions. *Human Brain Mapping*, *7*, 254–266.

Breiter, H. C., Aharon, I., Kahneman, D., & Dale, A. (2001). Functional Imaging of neural responses to expectancy and experiences of monetary gains and losses. *Neuron*, *30*, 619–639.

Courtney, S. M., Ungerleider, L. G., Keil, K., & Haxby, J. V. (1997). Transient and sustained activity in a distributed neural system for human working memory. *Nature*, *386*(6625), 608–611.

Critchley, H. D., Mathias, C. J., & Dolan, R. J. (2001). Neural activity in the human brain relating to uncertainty and arousal during anticipation. *Neuron*, *29*, 537–545.

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

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., Rees, G., & Dolan, R. J. (1999). Ventromedial prefrontal cortex mediates guessing. *Neuropsychologia*, *37*, 403–411.

Friston, K. J., Holmes, A. P., Worsley, K. J., Poline, J. B., Frith, C. D., & Frackowiak, R. S. J. (1995). Statistical parametric maps in functional imaging: A general linear approach. *Human Brain Mapping*, *2*, 189–210.

Gazzaniga, M. S. (2000). Cerebral specialization and interhemispheric communication: Does the corpus callosum enable the human condition? *Brain*, *7*, 1293–1326.

Gilovich, T., Vallone, R., & Tversky, A. (1985). The hot hand in basketball: On the misperception of random sequences. *Cognitive Psychology*, *17*(3), 295–314.

Gruber, O., Kleinschmidt, A., Binkofski, F., Steinmetz, H., & von Cramon, D. Y. (2000). Cerebral correlates of working memory for temporal information. *NeuroReport*, *11*(8), 1689–1693.

Hinson, J. M., & Staddon, J. E. R. (1983). Matching, maximizing and hillclimbing. *Journal of the Experimental Analysis of Behavior*, *40*, 321–331.

Huettel, S. A., Mack, P. B., & McCarthy, G. (2002). Perceiving patterns in random series: Dynamic processing of sequence in prefrontal cortex. *Nature Neuroscience*, *5*(5), 485–490.

Jaeggi, S. M., Seewer, R., Nirkko, A. C., Eckstein, D., Schroth, G., Groner, R., et al. (2003). Does excessive memory load attenuate activation in the prefrontal cortex? Load-dependent processing in single and dual tasks: Functional magnetic resonance imaging study. *NeuroImage*, *19*, 210–225.

Kahneman, D., & Tversky, A. (1973). On the psychology of prediction. *Psychological Review*, *80*, 237–251.

Kwong, K. K., Belliveau, J. W., Chesler, D. A., Goldberg, I. E., Weiskoff, R. M., Poncelet, B. P., et al. (1992). Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proceedings of the National Academy of Science*, *89*, 5675–5679.

Leung, H.-C., Gore, J. C., & Goldman-Rakic, P. S. (2002). Sustained mnemonic response in the human middle frontal gyrus during on-line storage of spatial memoranda. *Journal of Cognitive Neuroscience*, *14*(4), 659–671.

McCarthy, G., Blamire, A. M., Puce, A., Nobre, A. C., Bloch, G., Hyder, F., et al. (1994). Functional magnetic resonance imaging of human prefrontal cortex activation during a spatial working-memory task. *Proceedings of the National Academy of Sciences of the United States of America*, *91*, 8690–8694.

Miller, M. B., & Valsangkar-Smyth, M. Probability matching in the right hemisphere. *Brain and Cognition*, in press.

Miller, M. B., Van Horn, J., Wolford, G. L., Handy, T. C., Valsangkar-Smyth, M., Inati, S., et al. (2002). Extensive individual differences in brain activations during episodic retrieval are reliable over time. *Journal of Cognitive Neuroscience*, *14*(8), 1200–1214.

O'Doherty, J. O., 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.

Ogawa, S., Tank, D. W., Menon, R., Ellermann, J. M., Kim, S. G., Merkle, H., et al. (1992). Intrinsic signal changes accompanying sensory stimulation: Functional brain mapping with magnetic resonance imaging. *Proceedings of the National Academy of Science*, *89*, 5951–5955.

Owen, A. M., Doyon, J., Petrides, M., & Evans, A. C. (1996). Planning and spatial working memory: A positron emission tomography study in humans. *European Journal of Neuroscience*, *8*, 353–364.

Paulus, M. P., Hozack, N., Zauscher, B., McDowell, J. E., Frank, L., Brown, G. G., et al. (2001). Prefrontal, parietal, and temporal cortex networks underlie decision-making in the presence of uncertainty. *NeuroImage*, *13*, 91–100.

Petrides, M., Alivisatos, B., Evans, A. C., & Meyer, E. (1993). Dissociation of human mid-dorsolateral from posterior dorsolateral frontal cortex in memory processing. *Proceedings of the National Academy of Sciences of the United States of America*, *90*(3), 873–877.

Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences*, *98*, 676–682.

Rogers, R. D., Owen, A. M., Middleton, H. C., Williams, E. J., Pickard, J. D., Sahakian, B. J., et al. (1999). Choosing between small, likely rewards and large, unlikely rewards activates inferior and orbital prefrontal cortex. *Journal of Neuroscience*, *19*, 9029–9038.

Rypma, B., Berger, J. S., & D'Espostio, M. (2002). The influence of working-memory demand and subject performance on prefrontal cortical activity. *Journal of Cognitive Neuroscience*, *14*(5), 721–731.

Schacter, D. L., & Wagner, A. D. (1999). Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval. *Hippocampus*, *9*(1), 7–24.

Schubotz, R. I., & von Cramon, D. Y. (2002). Predicting perceptual events activates corresponding motor schemes in lateral premotor cortex: An fMRI study. *NeuroImage*, *15*, 787–796.

Volz, K. G., Schubotz, R. I., & von Cramon, D. Y. (2003). Predicting events of varying probability: Uncertainty investigated by fMRI. *NeuroImage*, *19*, 271–280.

Wig, G. S., Miller, M. B., Kingstone, A., & Kelley, W. M. (2004). Seperable routes to human memory formation: dissociating task and material contributions in the prefrontal cortex. *Journal of Cognitive Neuroscience*, *16*(1), 139–148.

Wolford, G., Miller, M. B., & Gazzaniga, M. S. (2000). The left hemisphere's role in hypothesis formation. *Journal of Neuroscience*, *20*(RC64), 1–4.

Wolford, G. L., Newman, S. E., Miller, M. B., & Wig, G. S. (2004). Searching for patterns in random sequences. *Canadian Journal of Experimental Psychology*.