

Dissociating the Roles of Right Ventral Lateral and Dorsal Lateral Prefrontal Cortex in Generation and Maintenance of Hypotheses in Set-shift Problems

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Although patient data have traditionally implicated the left prefrontal cortex (PFC) in hypothesis generation, recent lesion data implicate right PFC in hypothesis generation tasks that involve set shifts (lateral transformations). To test the involvement of the right prefrontal cortex in a hypothesis generation task involving set shifts, we scanned 13 normal subjects with fMRI as they completed Match Problems (a classic divergent thinking task) and a baseline task. In Match Problems subjects determined the number of possible solutions for each trial. Successful solutions are indicative of set shifts. In the baseline condition subjects evaluated the accuracy of hypothetical solutions to match problems. A comparison of Match Problems versus baseline trials revealed activation in right ventral lateral PFC (BA 47) and left dorsal lateral PFC (BA 46). A further comparison of successfully versus unsuccessfully completed Match Problems revealed activation in right ventral lateral PFC (BA 47), left middle frontal gyrus (BA 9) and left frontal pole (BA 10), thus identifying the former as a critical component of the neural mechanisms of set-shift transformation. By contrast, activation in right dorsal lateral PFC (BA 46) covaried as a function of the number of solutions generated in Match Problems, possibly due to increased working memory demands to maintain multiple solutions 'on-line', conflict resolution, or progress monitoring. These results go beyond the patient data by identifying the ventral lateral (BA 47) aspect of right PFC as being a critical component of the neural systems underlying lateral transformations, and demonstrate a dissociation between right VLPFC and DLPFC in hypotheses generation and maintenance.

Keywords: divergent thinking, hypothesis generation, lateral transformation, problem solving, set shift

Introduction

While much patient data implicates the left prefrontal cortex in thinking and problem solving (Gazzaniga, 2000), some recent evidence indicates that lesions to the right prefrontal cortex (PFC) can result in subtle but profound deficits in real-world problem solving, even while leaving standard neuropsychological test profiles largely intact. For example, Shallice and Burgess (1991) described three frontal lobe patients, with WAIS-R scores ranging from 120 to 130, who experienced severe organizational difficulties in two simple but open-ended laboratory tasks (Multiple Errands Test and Six Elements Test) that were designed to mimic problem solving under conditions of low external constraints. Goel and Grafman (2000) described a very accomplished architect with a right hemisphere lesion, who scored 128 on the WAIS-R, but was simply unable to cope in the world. In a large patient study Burgess *et al.* (2000) tested the performance of 60 patients with focal brain damage and 60 age- and education-matched controls on the Greenwich Test,

and concluded that the right PFC may have a critical role to play in planning in open-ended tasks (see also Burgess, 2000). There is, however, little agreement as to exactly what aspect(s) of real-world problem solving these patients are having difficulty with (Shallice, 1988; Damasio, 1994; Goldman-Rakic, 1994; Grafman, 2002). Indeed, given the variability of lesion locations within these patients, it is very likely that the 'real-world' coping difficulties described in these studies are manifestations of several types of cognitive and emotional deficits.

Goel and Grafman (2000) have suggested that the issue with their patient was one of dealing with the lack of facilitating environmental structure. They tested an accomplished 57-year-old architect with a right prefrontal lesion (patient PF), by requiring him to develop a new design for a lab space, and compared his performance to an age- and education-matched architect. By having the subjects engage in verbal protocol analysis (Ericsson and Simon, 1993) and undertaking a detailed mapping of their respective problem spaces (Newell and Simon, 1972), they were able to show that the patient's sophisticated architectural knowledge base and drawing ability were still intact, and that he used them quite skilfully during the problem-structuring phase. PF's ability to evaluate given solutions to architectural problems was also unaffected, and he discussed the issues with eloquence and sophistication. However, his problem-solving behavior differed from the control's in that he fixated on the plan of the existing lab space, and his generation of kernel ideas or solution fragments was minimal and erratic. PF's difficulties were identified as (i) an inability to generate solutions in the absence of guiding constraints or patterns that can be extrapolated; and (ii) an inability to engage in the 'lateral transformations' necessary for breaking away (set-shifting) from the present state of affairs (i.e. the existing lab organization) and proposing and developing potential solutions. The focus of the present study is to verify the involvement of right PFC in set-shifting lateral transformations.

A 'lateral transformation' is a movement from one state in a problem space to a horizontally displaced state rather than a more detailed version of the same state (i.e. vertically displaced state). Goel (1995) has proposed that lateral transformations are facilitated or hindered by the structure of mental representations. Representations that are imprecise, ambiguous, fluid, indeterminate, vague, etc., facilitate lateral transformations. Mental representations that are overly precise and concrete can hinder lateral transformations, though they are necessary for other aspects of problem solving (see Goel, 1995). For example, an ambiguous or overlapping mental state token (e.g. mental token of the duck-rabbit illusion) introduces a degree of coarseness into the problem space by allowing a single state to simultaneously instantiate two ideas in a non-complex

or primitive manner. This allows the problem solver to remain non-committal about the state he/she is in and easily move between them. Lateral transformations are necessary for overcoming set effects and facilitate *widening* of the problem space. Goel (2002) has further suggested that processing these vague, indeterminate or 'ill-structured' representations may involve the right PFC. Related claims have been made more generally about the right hemisphere (Goldberg *et al.*, 1994; Jung-Beeman *et al.*, 2004; but see Poldrack *et al.*, 2001).

To test the involvement of PFC in the generation of lateral transformations, we utilized Guilford's (1967) Match Problems task. This is a classic divergent thinking problem that has been studied extensively in various forms at least since Katona (1940). In essence, it involves an arrangement of matches that must be reorganized to make other patterns by removing matches (Fig. 1). An important requirement is that the final pattern must not contain any incomplete squares. Like all problems, it can be characterized by an initial state, a goal state and a transformation function that maps the initial state onto the goal state. The start state in Match Problems is completely and unambiguously characterized by the given pattern of matches. The goal state is specified in terms of an abstract rule that can map onto an unknown number of specific patterns. The transformation function is also specified, and on the surface seems trivial — remove a specified number of matches (either sequentially or simultaneously). The task is to apply this transformation function in a generate-and-evaluate cycle to make patterns that satisfy the rule.

The Match Problems task is an interesting problem for present purposes because the application of the transformation function is complicated by the fact that the start state pattern provides a strong mental set that implicitly obstructs/hinders certain transformations. Consider the simple example in Figure 1: 'Remove one match to make seven squares.' Having observed many subjects do this problem, we know that most will begin by trying to remove sticks A, E, N, S, V, R, I or D. These transformations are unsatisfactory because removing one of these matchsticks leaves one incomplete square, and thus does not completely satisfy the rule. Another possibility is to remove matchsticks J, K, L or M. This however, leaves six squares and one rectangle. Again, this does not completely satisfy the rule. Many subjects stop at this point and conclude that the rule cannot be satisfied. The solution is to remove one of B, C, T or U.

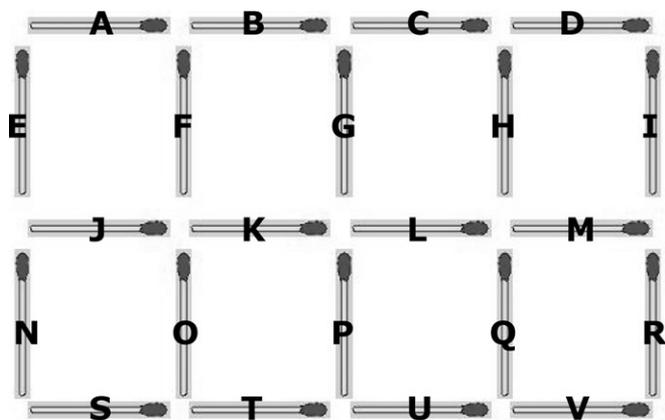


Figure 1. The 22-match formation that formed the basis of each trial in Match Problems (note that the letters are added for the purpose of aiding discussion in the text).

This trivial solution does not occur to many subjects, presumably because the removal of one of these sticks leaves a gap in the otherwise continuous figure. Nothing in the task instructions requires that the contiguity of the squares be maintained. However, maintaining contiguity is implicitly enforced by the mental set created by the explicit concrete representation of the start state pattern. (The size of squares is another implicitly enforced constraint.) It has been long recognized that successful solutions to Match Problems require 'set shifts' to overcome such fixation (Guilford, 1967). These set shifts are isomorphic to Goel's (1995) lateral transformations introduced above, and will be facilitated by a mental representation of the start state that is more abstract and ambiguous than the one provided in the problem statement.

To verify the role of right PFC in mental set-shifts we scanned 13 normal subjects as they solved the Match Problems task and a baseline task. In the former, subjects engaged in generate-and-evaluate cycles to determine the number of ways in which the rule specified goal state could be achieved. In fact, the *number* of solutions generated in response to open-ended problems has been shown to be the most important factor in divergent thinking tasks (Plucker and Renzulli, 1999). Successful generate-and-evaluate cycles are indicative of lateral transformations or set shifts. In the baseline task subjects evaluated a given solution to a match problem to see if it satisfied the given rule. We reasoned that because Match Problems involve the generation and evaluation of hypotheses, whereas the baseline task only involves evaluating given hypotheses, a comparison of the two processes would reveal those brain regions involved in the generation of hypotheses in set-shift problems. Furthermore, a comparison of successfully completed with unsuccessfully completed Match Problems will isolate brain regions involved specifically in lateral transformations or set shifts.

Materials and Methods

Subjects

Thirteen right-handed subjects (eight females) with no history of neurological disorders participated in this study. The mean age of the sample was 26.3 years (SD = 3.9), and the mean education level was 17.2 years (SD = 1.6). The study was approved by the Human Participants Review Sub-Committee of York University, and all subjects gave informed consent.

Materials and Procedure

The items generated for this study were variations of the original Match Problems developed to measure divergent thinking (Guilford, 1967). Two different conditions were prepared: Match Problems and baseline. Each condition contained 20 items, with no repetition within or between the two conditions. On each trial of Match Problems an identical 22-match formation that included eight fully formed squares was presented to subjects (Fig. 2). Underneath the matches, a caption instructed subjects to remove a specified number of matches in order to generate a specified number of fully formed squares. On each trial the subjects' task was to determine the number of ways in which the instruction (rule) could be satisfied. Possible responses ranged from 0 to 4, and subjects were instructed to press the button that corresponded to the correct number of solutions to the problem. Ten trials contained no solutions, whereas the remaining ten trials contained either two or four possible solutions (subjects were not made aware of this proportional breakdown). The ten match problems that were soluble required set shifts that consisted of either the generation of solutions that involved non-contiguous squares (such as the example discussed in the Introduction), or the generation of squares that varied in size.

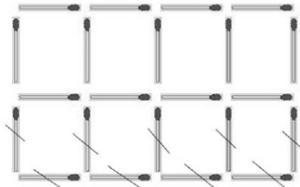
On each trial of the baseline condition a 22-match formation that included eight fully formed squares was presented to subjects (Fig. 2).

- Match Problems



Remove 1 Match
Make 7 Squares

- Baseline



Remove 9 Matches
Make 4 Squares

Figure 2. Sample trials from Match Problems (accurate response is '4') and the baseline condition (accurate response is 'Correct').

Underneath the matches, a caption appeared that instructed subjects to remove a specified number of matches in order to generate a specified number of fully formed squares. However, in contrast to Match Problems, the specified number of matches had already been crossed out. The subjects' task was to determine whether the provided option constituted a correct solution to the problem. The subject was instructed to press one of two buttons corresponding to either 'Correct' or 'Incorrect'. The options provided on ten trials were correct, and on the remaining ten trials incorrect (subjects were not made aware of this proportional breakdown).

The trials for both conditions were 15 s in length, and were structured as follows: at $t = 0$, the slide containing the 22-match formation and the instruction caption appeared on the monitor. Subjects were instructed to enter their response as soon as they had solved the problem. At $t = 12$ s, a red '?' appeared at the bottom right-hand corner of the slide, indicating to subjects that if they had not entered a response already, they had 3 s to do so. This procedure was used because a pilot study had demonstrated that due to immersion in the task, subjects sometimes lost track of time and did not enter their responses prior to the termination of trials. In the pilot study, the addition of '?' at the 12 s mark nearly eliminated the number of trials on which subjects failed to enter a response. As such, it was incorporated into the design of the experiment. In the scanner, the order in which Match Problems and the baseline condition were administered, as well as the hand that was used to enter responses, were counterbalanced. The stimuli were presented to the subjects using a LCD projector (NEC MultiSync MT800) with a video resolution of 640×480 pixels, and a light output of 370 lumens.

fMRI Scanning and Data Analysis

A 4T Oxford Magnet Technologies magnet with a Siemens Sonata gradient coil was used to acquire T_1 anatomical volume images ($1 \times 1 \times 2$ mm voxels) and 22 T_2^* -weighted interleaved multi-shot contiguous echoplanar images ($3 \times 3 \times 5$ mm voxels), sensitive to blood oxygenation level dependent (BOLD) contrast. The images were acquired axially and positioned to cover the whole brain. Data were recorded during a single acquisition period. A total of 106 volume images were acquired, with a repetition time (T_R) of 3 s/vol. The first six volumes were discarded to allow for T_1 equilibration effects (leaving 100 volumes per session).

Data were analyzed using Statistical Parametric Mapping (SPM2) (Friston *et al.*, 1995). All functional volumes were spatially realigned to the first volume. Head movement was < 2 mm in all cases. A mean image created from the realigned volumes was spatially normalized to the

Montreal Neurological Institute EPI brain template (Evans *et al.*, 1993) using nonlinear basis functions (Ashburner and Friston, 1999). The derived spatial transformation was then applied to the realigned T_2^* volumes, which were finally spatially smoothed with a 12 mm FWHM isotropic Gaussian kernel [in order to make comparisons across subjects and to permit application of random field theory for corrected statistical inference (Worsley and Friston, 1995)]. The resulting time series across each voxel were high-pass filtered with a cut-off of 128 s, using cosine functions to remove section-specific low frequency drifts in the BOLD signal. Global means were normalized by proportional scaling to a grand mean of 100.

Condition effects at each voxel were estimated according to the general linear model and regionally specific effects compared using linear contrasts. Each contrast produced a statistical parametric map of the t -statistic for each voxel, which was subsequently transformed to a unit normal Z -distribution. The activations reported survived a voxel-level intensity threshold of $P < 0.05$ using a random effect model, corrected for multiple comparisons using false discovery rate (Genovese *et al.*, 2002), and a minimum cluster size of 15 contiguous voxels. Given the general *a priori* expectations about left PFC involvement in problem solving (Gazzaniga, 2000), and our specific *a priori* hypothesis about the involvement of right PFC in the generation task, the correction space for activation in left PFC was limited to the left PFC, and the correction space for activation in right PFC was limited to the right PFC. The BOLD signal was modeled as a box-car of 15 s duration, convolved with a canonical hemodynamic response function. The presentation of the '?' sign and the subjects' motor responses were modeled out as events of no interest.

Results

Behavioral Results

Two types of behavioral results were obtained: reaction time and accuracy. The average reaction time for the baseline condition was 12 545 ms (SD = 284). The average reaction time for Match Problems was 13 326 ms (SD = 489). The difference in reaction time between Match Problems and baseline was significant, $t(12) = 9.18$, $P < 0.001$. Accuracy scores were calculated as follows. Recall that in the baseline condition the range of possible responses was dichotomous (correct versus incorrect). Across all subjects, 74% of responses were accurate. This percentage was significantly higher than chance, $t(12) = 4.11$, $P < 0.01$. Accuracy was calculated differently for Match Problems. On those ten trials where the accurate response was '0' (i.e. no possible solution), any other response was considered to be inaccurate. On the remaining ten trials, accuracy was calculated as the ratio of the entered response to the total number of possible solutions. For example, if a problem embodied four possible solutions, a response of '3' was considered to be 0.75 accurate. Accuracy was calculated in this way because to discover three solutions to a four-solution problem is not inaccurate, but rather incomplete. It should be noted that our design did not allow for direct verification of the accuracy of entered responses. Therefore, to minimize the likelihood of incorrect solutions contaminating responses, if the entered response exceeded the total number of possible solutions, the trial was considered inaccurate. Across all subjects, 50% of responses were accurate. This percentage was significantly higher than chance, $t(12) = 6.33$, $P < 0.01$. The difference in accuracy rates between Match Problems and baseline was significant, $t(12) = -3.63$, $P < 0.01$.

Functional MRI Results

To test our hypothesis of PFC involvement in lateral transformations, we did a direct comparison of Match Problems

versus baseline trials. For this analysis, the 15 s duration of each trial was modeled as an epoch. Motor response and the appearance of '?' at the 12 s mark were modeled as events of no interest. In addition, behavioral results demonstrated that subjects were less accurate and required a longer amount of time to solve Match Problems. This implied that any neuroanatomical difference between Match Problems and baseline trials might be due to a higher level of difficulty associated with the former condition. To counteract this possibility, Match Problems and baseline trials were administered to 33 psychology undergraduates outside of the scanner. Based on this sample's average accuracy and reaction time results, the problems in each condition were grouped into four difficulty categories (1-4), ranging from easy (1) to difficult (4). These difficulty ratings were in turn entered into the analysis as covariates of no interest. A comparison of Match Problems versus baseline trials revealed significant activation in left dorsal lateral PFC (BA 46) (-32, 34, 46, $z = 3.58$) and right ventral lateral PFC (BA 47) (32, 28, -16, $z = 3.26$), corrected for multiple comparisons when the space of possibilities was confined to left and right PFC respectively, as per our hypothesis (Fig. 3). The identity of the latter was confirmed by the guidelines provided by Chiavaras *et al.* (2001). The reverse comparison of baseline versus Match Problems did not reveal any area of significant activation. To

determine areas common to both conditions, we inclusively masked the baseline condition with Match Problems. The result revealed significant activation in right occipital gyrus (BA 18) (30, -94, 0, $z = 4.77$).

The above comparison of Match Problems versus baseline trials isolates brain regions involved in hypotheses generation in set-shift problems. This generation process will include both lateral and non-lateral transformations. To specifically identify the neural correlates of lateral transformations, we isolated match problems that had correct solutions and compared those for which at least one correct solution was generated versus those for which no correct solution was generated (Successful versus Unsuccessful). This resulted in activation in right ventral lateral PFC (BA 47) (34, 14, -18, $z = 4.20$), left middle frontal gyrus (BA 9) (-26, 40, 28, $z = 3.53$), and left frontal pole (BA 10) (-16, 58, 10, $z = 3.48$). A further comparison of unsolved match problems (that had correct solutions) versus baseline trials revealed no areas of significant activation. Next, we conducted a conjunction analysis to determine areas of activation that were common to the Match Problems versus baseline and Successful versus Unsuccessful contrasts, and the results revealed significant activation in right ventral lateral PFC (BA 47) (34, 16, -16, $z = 4.18$), left middle frontal gyrus (BA 9) (-28, 40, 28, $z = 3.49$), and left frontal pole (BA 10) (-18, 56, 12, $z = 3.38$).

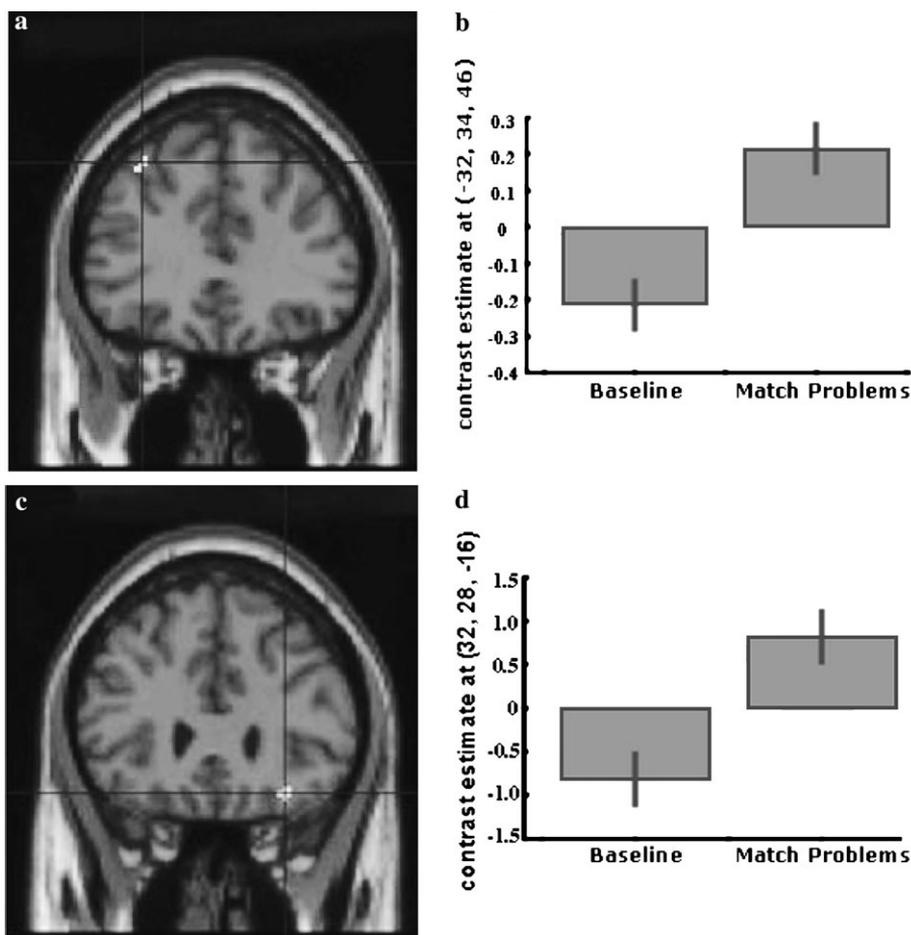


Figure 3. A comparison of Match Problems versus baseline trials revealed significant activation in (a) left dorsal lateral PFC (BA 46) (-32, 34, 46, $z = 3.58$), and (c) right ventral lateral PFC (BA 47) (32, 28, -16, $z = 3.26$). SPMs rendered into standard stereotactic space and superimposed on to coronal MRIs in standard space. Regions are designated using MNI coordinates. Condition specific parameter estimates demonstrate that (b) left dorsal lateral PFC (-32, 34, 46) is relatively more activated in Match Problems compared to the baseline condition, and that (d) right ventral lateral PFC (32, 28, -16) is relatively more activated in Match Problems compared to the baseline condition.

In our final analysis we examined the proportion of responses that were generated on each trial of Match Problems. For each subject, a new vector was created using two steps. First, the response on each trial was converted to a ratio of possible solutions (using the procedure described above). Second, each ratio score was converted to a deviation score (from the mean ratio score of the subject). The 15 s duration of each trial was modeled as an epoch. Motor response and the appearance of '?' at the 12 s mark were modeled as events of no interest. The deviation scores were entered as covariates in a parametric analysis of fMRI data. The results revealed that activation in right dorsal lateral PFC (BA 46) (48, 38, 24, $z = 4.82$) and cerebellum (-4, -94, -22, $z = 5.11$) covaried as a function of the number of solutions that were generated in response to match problems (Fig. 4).

Discussion

In Match Problems subjects were instructed to determine the number of ways in which trials could be solved. The task required subjects to generate and evaluate multiple hypotheses. In successful trials, hypotheses generation would involve set shifts or lateral transformations. By contrast, in the baseline condition subjects were instructed to evaluate the accuracy of given solutions to match problems, without the requirement of generating any hypotheses. Engagement in Match Problems

(generate and evaluate cycles) relative to baseline trials (evaluate cycles) resulted in significant activation in left dorsal lateral PFC (BA 46) and right ventral lateral PFC (BA 47). These activations can be attributed to either the generation of hypotheses, the generation of set-shift hypotheses, or both. However, the additional comparison (within Match Problems that had correct solutions) of successfully completed (some lateral transformations) with unsuccessfully completed (no lateral transformation) trials also resulted in activation in right ventral lateral PFC (BA 47), along with activations in left middle frontal gyrus (BA 9) and left frontal pole (BA 10). This suggests that a bilateral prefrontal neural system underwrites hypothesis generation involving set-shift transformations, and that right ventral lateral PFC (BA 47) is a critical component of this neural system.

The critical role of the right ventral PFC is reinforced by a study of 53 patients with focal brain lesions and 20 normal controls on Match Problems tasks (Miller and Tippett, 1996). Miller and Tippett (1996) administered two types of match problems to their subjects. One type required set shifting to arrive at correct solutions, whereas the other type consisted of problems that required straightforward match removal for solution. They reported that patients with focal right PFC lesions were impaired specifically on those match problems that required set shifts. This selective impairment in performance was especially apparent in patients with lesions to right

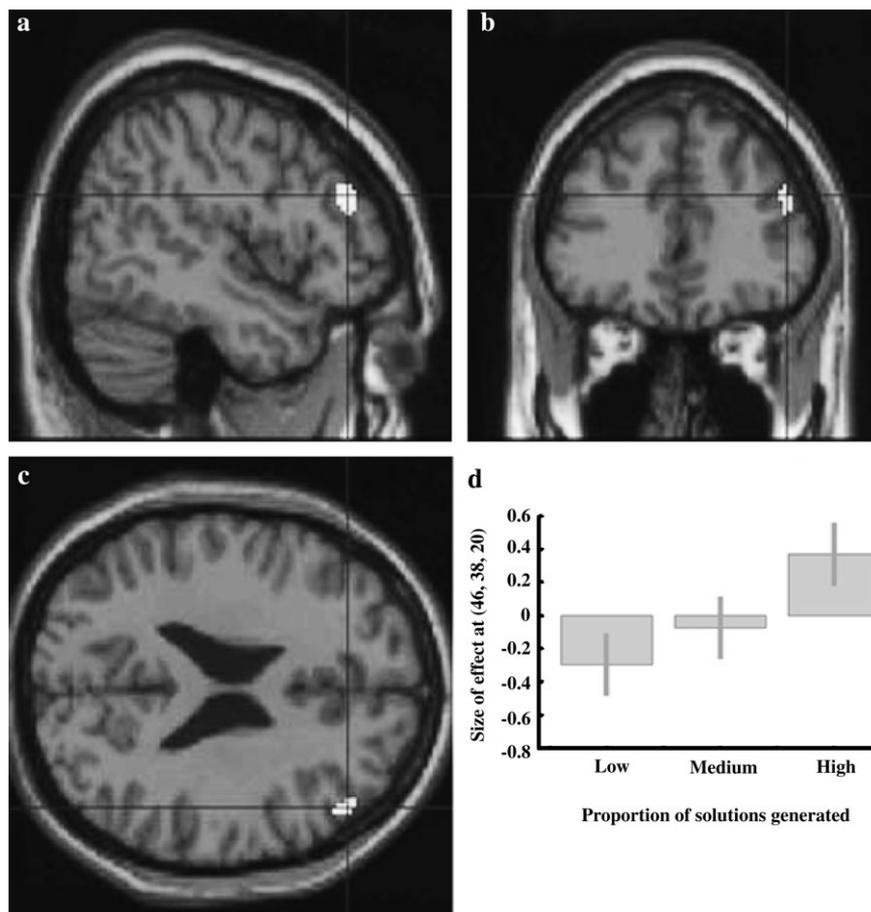


Figure 4. Activation in right dorsal lateral PFC (BA 46) (48, 38, 24, $z = 4.82$) covaried as a function of the number of solutions in Match Problems. SPMs rendered into standard stereotactic space and superimposed on to (a) sagittal, (b) coronal and (c) transverse standard space. Region is designated using MNI coordinates. (d) Condition specific parameter estimates demonstrate that activation in right dorsal lateral PFC (46, 38, 20) increases in response to generating low, medium and high proportion of solutions in Match Problems.

ventral (as opposed to dorsal) PFC, suggesting that this region is not only critical but necessary for set-shift transformations.

Our results are consistent with and expand upon not only the lesion data (Miller and Tippett, 1996; Burgess, 2000; Goel and Grafman, 2000), but also findings from neuroimaging studies. For example, Luo *et al.* (2003) reported activation in right lateral orbital PFC (BA 47; 39, 29, -13) in a verbal analogical reasoning task that required subjects to generate and evaluate a solution to the analogical relationship between two pairs of words (e.g. soldier-army; drummer-band) compared to a simple semantic comprehension condition. This task is similar to ours in that it involves generate/evaluate cycles defined over start states where overly concrete representations could obscure or hinder transformations. A successful solution requires subjects to abstract away from the literal/concrete meaning of the given word pair (start state) and search for an abstract relationship. Insofar as subjects cannot abstract away from the concrete meanings, the pattern will obstruct the solution. It is also noteworthy that Luo *et al.*'s (2003) study involved linguistic stimuli, while the present study involves pictorial stimuli suggesting that the involvement of right inferior PFC is not modality specific, but rather task specific. This is consistent with recent claims that hemispheric asymmetry is task rather than modality specific (Stephan *et al.*, 2003).

It is also possible to argue that the activation in right ventral lateral PFC associated with successful versus unsuccessful solution of match problems may be due to an experience of insight, rather than hypothesis generation involving lateral transformations. This interpretation is weakened by the lesion data (Miller and Tippett, 1996) and the fact that several imaging studies have associated activation in right temporal lobe structures with the experience of insight (Schneider *et al.*, 1996; Luo and Niki, 2003; Jung-Beeman *et al.*, 2004), and have failed to activate right ventral lateral PFC (BA 47). Luo and Niki (2003), for example, presented subjects with Japanese riddles that they knew they could not solve (e.g. 'The thing that can move heavy logs, but cannot move a small nail'), and then presented them with the answer (i.e. river) in order to generate an experience of insight. The results showed that activation in right hippocampus, not right PFC, was associated with the experience of insight.

At first glance, our focus on right PFC as having a critical role in hypothesis generation — even 'set shifting' transformations — appears inconsistent with at least two lines of research in the neuropsychology literature. With respect to hypothesis generation, Gazzaniga (1998) has argued that following surgical division of the hemispheres, the ability of the left hemisphere to engage in problem solving and reasoning remains intact, whereas the ability of the right hemisphere is seriously impoverished. In a recent demonstration of this, Wolford *et al.* (2000) tested the performance of split-brain and focal lesion patients in a task where they were required to predict the occurrence of events based on exposure to previously presented sequences. The results showed that the left hemisphere is more adept at extracting patterns from past sequences than the right hemisphere. Based on such data, Gazzaniga postulates the existence of a structure called the 'interpreter' in the left hemisphere whose function is to make sense of the environment by extracting patterns — causal, logical, statistical — from events. Indeed, our lab has accumulated considerable evidence to support the critical role of the left PFC in extracting logical patterns in reasoning tasks (Goel *et al.*, 1998, 2000, 2004; Goel and Dolan, 2003, 2004).

With respect to 'set shifts', perseverative errors in the Wisconsin Card Sorting Test (WCST) can be viewed as a form of 'rule shift' failure. There are reports that left PFC lesions result in perseverative errors on WCST-type tasks (Milner, 1971; Rogers *et al.*, 1998), and recent neuroimaging studies seem to support this conclusion (Konishi *et al.*, 2002; see also Cools *et al.*, 2004), though other studies suggest a role for right PFC in such rule shifts (Lombardi *et al.*, 1999; Jimura *et al.*, 2004).

However, there are critical differences between hypotheses generation and 'set shifts' in these tasks and the divergent thinking tasks to which the Match Problem belongs. Specifically, Gazzaniga's pattern extrapolation tasks either contain facilitative patterns (real or imaginary) that can be locked onto and extrapolated for successful solution, or at least do not contain built-in hindrances to pattern extraction. In such cases the left hemisphere interpreter may be necessary and sufficient for hypothesis generation (Goel *et al.*, 2000; Goel and Dolan, 2003). By contrast, the start state pattern in set-shift Match Problems actually obstructs/hinders search through the problem space, requiring lateral transformations for successful solution. We are suggesting that when the initial state space representations are obscure or obstructive, the left hemisphere 'interpreter' may still be necessary — as evidenced by our left PFC activation — but will not be sufficient for the task. When a recognizable pattern or structure cannot be readily extracted from the task environment, or if the pattern is actually obstructive to the solution (as in the case of Match Problems), the right PFC plays a necessary role in generating possibilities that can aid in navigating through the problem space. It does so by supporting the encoding and processing of ill-structured representations (Goel, 1995).

Perseverative errors in the WCST have been used as an index of cognitive flexibility. Cognitive flexibility can be viewed as a form of 'mental set shifting'. However, the similarity between 'mental set shifts' required by the WCST and Match Problems is superficial. Specifically, making few perseverative errors in WCST indicates flexibility in response to environmental feedback. It does not indicate a spontaneous ability to overcome implicit constraints and engage in the divergent production of new strategies (i.e. lateral transformations). In recognition of this difference, cognitive flexibility in the context of WCST has been termed *reactive*, whereas cognitive flexibility in the context of divergent thinking tasks has been termed *spontaneous* (Eslinger and Grattan, 1993). Cognitive flexibility in response to environmental feedback may be necessary — as evidenced by our left PFC activation — but is not sufficient for set shifting lateral transformations as captured by tests of divergent thinking, like Match Problems (Goel, 1995). Again, our position is that the right PFC is playing a critical, even necessary (though not sufficient) role in facilitating these lateral transformations.

In addition to the right ventral lateral PFC activation during set-shift transformations, we also found that activation in right dorsal lateral PFC (BA 46) covaried with the *number* of solutions generated in Match Problems trials (Fig. 4). There are several possible explanations for this. First, an inevitable consequence of generating additional hypotheses in divergent trials is the requirement to maintain them in working memory (WM) until the end of the trial. Each hypothesis needs to be maintained in WM while the next is being generated so as not to regenerate previous ones. The involvement of right dorsal lateral PFC in WM (Thomas *et al.*, 1999; Braver *et al.*, 2001), in

Table 1

A complete list of activations for all comparisons

Comparison and region of activation	BA	L	Z-score	x	y	z
Match Problems–baseline						
Dorsal lateral PFC	46	L	3.58	−32	34	46
Ventral lateral PFC	47	R	3.26	32	28	−16
Baseline masked inclusively with Match Problems						
Occipital gyrus	18	R	4.77	30	−94	0
Successful versus unsuccessful Match Problems						
Ventral lateral PFC	47	R	4.20	34	14	−18
Middle frontal gyrus	9	L	3.53	−26	40	28
Frontal pole	10	L	3.48	−16	58	10
Conjunction of Match Problems–baseline with Successful versus unsuccessful Match Problems						
Ventral lateral PFC	47	R	4.18	34	16	−16
Middle frontal gyrus	9	L	3.49	−28	40	28
Frontal pole	10	L	3.38	−18	56	12
Areas where activation covaried with the number of solutions in Match Problems						
Dorsal lateral PFC	46	R	4.82	48	38	24
Cerebellum	−	L	5.11	−4	−94	−22

The reverse comparisons (baseline–Match Problems, unsuccessful–successful Match Problems) did not result in any significant area of activation. Regions are designated using the MNI coordinates. BA indicates Brodmann area. L indicates laterality.

particular in maintaining and storing information, is a stable finding in neuroscience and extends across both verbal and spatial modalities (Barch *et al.*, 1997; Cohen *et al.*, 1997; Leung *et al.*, 2002; Zurovski *et al.*, 2002).

Another possible explanation for the activation in right dorsal lateral PFC (BA 46) is that it may be involved in monitoring of sub-goal processes (Braver and Bongiolatti, 2002). Sub-goal processing is a hallmark of many higher-level cognitive tasks such as planning, reasoning and problem solving that involve sequential processing and monitoring of relations. In the context of Match Problems, the higher-order task is to determine the number of ways in which a rule (instruction) can be satisfied. As subjects generate and evaluate hypotheses, they need to keep track of successful attempts (so they can be added to the total and not repeated) as well as unsuccessful attempts (so they are not repeated). On a cognitive level, one would expect a positive correlation between the number of hypotheses generated/evaluated and the demand on monitoring resources and relations. In fact, right BA 46 has been implicated in tasks that require the integration of multiple relations (Christoff *et al.*, 2001).

A third possibility for the observed activation in right dorsal lateral PFC (BA 46) involves conflict resolution. Consider a match problem that has four possible solutions. If a subject manages to generate only a single solution, ‘1’ will be entered as the response to the problem. However, as additional solutions are generated, not only is there a need to update previous responses, but also a conflict between the previous response, that is no longer correct (e.g. 1), and new response (e.g. 2, 3 or 4). As one generates more responses, the conflict of choosing between multiple responses would increase accordingly. The role of the right dorsal lateral PFC in conflict detection and/or resolution is widely recognized (Goel *et al.*, 2000; Pascual-Leone and Johnson, 2004). Of course, these three explanations of holding information in WM, progress monitoring and conflict resolution are not mutually exclusive.

This dissociation between right ventral lateral PFC and right dorsal lateral PFC is consistent with findings from an fMRI study

of the Tower of London task (Newman *et al.*, 2003). This study reported activation in right PFC — including right inferior frontal gyrus and dorsal lateral PFC — during plan generation. However, varying task difficulty (i.e. number of moves to solution), hence cognitive load, modulated activity in dorsal lateral PFC, but not in the right inferior frontal gyrus. This again suggests that right inferior frontal gyrus is involved in the generation of solutions per se, whereas the involvement of right dorsal lateral PFC is a function of cognitive load.

In summary, our findings demonstrate dissociation between hypotheses generation and maintenance, with hypothesis generation activating right ventral lateral PFC and left dorsal lateral PFC, and hypothesis maintenance activating right dorsal lateral PFC, a region implicated in WM, conflict detection, and cognitive monitoring tasks. The results regarding hypotheses generation are particularly interesting. Because right ventral lateral PFC was also activated in successful match problems, the results confirm a critical role for right PFC in the generation of lateral transformations as predicted by the lesion data (Miller and Tippett, 1996; Burgess, 2000; Goel and Grafman, 2000), and identify right ventral lateral PFC (BA 47) as being a key component of the neural generator of set shifts (lateral transformations). This of course does not imply that right ventral lateral PFC is sufficient for the task, as evidenced by the activation in left dorsal lateral PFC (BA 46) in the Match Problems versus baseline contrast, and the involvement of left middle frontal gyrus (BA 9) and left frontal pole (BA 10) in successful versus unsuccessful match problem trials. Comparison of our results with previous studies further suggests that the involvement of the right ventral lateral PFC in lateral transformations is modality independent.

Notes

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