

Task constraints modulate activation in right ventral lateral prefrontal cortex[☆]

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Lesion data suggest that right prefrontal cortex (PFC) plays a critical role in open-ended problem solving. To test this hypothesis, we scanned fifteen normal subjects with fMRI as they completed three types of anagram problems varying in the level of constraints placed on the search space. On unconstrained trials, they rearranged letters to generate solutions (e.g., Can you make a “Word with ZJAZ?”). On semantically constrained trials, they rearranged letters to generate solutions within particular semantic categories (e.g., Can you make a type of “Music with ZJAZ?”). On baseline trials, they rearranged letters to make specific words (e.g., Can you make the word “JAZZ with ZJAZ?”). As predicted, the critical comparison of unconstrained vs. semantically constrained trials revealed significant activation in right ventral lateral PFC, as well as left superior frontal gyrus, frontopolar cortex, right superior parietal lobe, right post central gyrus, and the occipital–parietal sulcus. Furthermore, activation in right ventral lateral PFC (BA 47) increased as the constraints placed on the anagram search space were reduced. We argue that the activation in right ventral lateral PFC is related to hypothesis generation in unconstrained settings, whereas activation in other structures is related to additional processes linked to anagram problems such as semantic retrieval, semantic categorization, and cognitive monitoring. These results extend the lesion data and imaging studies by demonstrating that a relative absence of constraints on the solution space is sufficient to engage right ventral lateral PFC in hypothesis generation tasks.

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Introduction

A number of neuropsychological studies have reported on the difficulties encountered by frontal lobe lesion patients – many of

them having lesions to the right prefrontal cortex – in real world problem solving, despite largely intact memory and IQ scores (Burgess, 2000; Eslinger and Damasio, 1985; Goel and Grafman, 2000; Goel et al., 1997; Shallice and Burgess, 1991). Real world problem solving is distinguished from most laboratory tests along at least a dozen dimensions (Goel, 1995). One of these dimensions is the lack of constraints on the solution path. There are usually very few hard external constraints to guide and facilitate search in real world problems. Lack of constraints does not necessarily make problems more difficult (Simon, 1973), but it does make them qualitatively different (Goel, 1995). Goel (2002) and Goel and Grafman (2000), have hypothesized that right PFC, and more recently right ventral lateral PFC (Goel and Vartanian, *in press*), is a critical component of a system involved in generating hypotheses in the absence of facilitating rules or guidelines (see also Burgess, 2000; Burgess et al., 2000; Goel and Dolan, 2000; Goldberg et al., 1994).

To study the effect of manipulating task constraints on right ventral lateral PFC, we used a variation of an anagram task (Metcalfe, 1986). Anagram problems require rearranging strings of letters (e.g., KEROLJ) to form words (JOKER). This task has a strong lexical but also a spatial component (letter arrangement). In his typology of problems, Greeno (1978) grouped anagrams under “arrangement problems.” Arrangement problems require the problem solver to arrange the elements of a problem in such a way as to satisfy a given criterion (for example, product must be a word). Greeno (1978) characterized the main skill in arrangement problems as “skill in composition, a process of constructive search, where the problem solver is required to find the solution in a search space but *must also know how to generate the possibilities that constitute the search space*” (p. 241) (emphasis added). This description underscores the critical role of generating hypotheses in solving anagrams (Newell and Simon, 1972; Dominowski, 1969; Gavurin, 1967a,b; Mendelsohn et al., 1966; Novick and Sherman, 2003; Ronning, 1965; Weisberg and Alba, 1981).

The hypothesis generation function can be usefully manipulated in anagram tasks. If we analyze the three components (start state, goal state, and transformation function) of an anagram problem in terms of information content (Goel, 1995; Reitman, 1964), we find that the start state is completely specified (e.g., ZJAZ). The goal

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state can be specified to different degrees, ranging from “can you make a word?” to “can you make a type of music?” to “can you make the word ‘jazz’?” Manipulating the goal state in this fashion also manipulates the transformation function. Where a goal state is specified in terms of a specific word, it becomes the de facto hypothesis, and the transformation function simply needs to evaluate the hypothesis by simple letter identification, rearrangement, and mapping. Where a goal state is specified in terms of a semantic category such as “type of music”, the transformation function can tap into a pattern or semantic knowledge base to generate and test a handful of likely candidates. Where the goal state is specified simply as “is a word”, there is no perceptible pattern or knowledge base to guide or facilitate the search. The transformation function can only rearrange letters until a recognized pattern emerges. This is a crucial distinction for our purposes. We will refer to the form of the first anagram problem as “constrained search”, the second as “semantically constrained search”, and the third as “unconstrained search.”

To directly test the hypothesis that generating hypotheses in an unconstrained situation involves right PFC, we scanned fifteen subjects using fMRI as they solved anagram tasks. The experiment employed the three types of trials discussed above (i.e., unconstrained, semantically constrained, constrained). Constrained trials were used as the baseline condition. Performance on unconstrained trials required subjects to generate potential solutions by rearranging letters, and to evaluate the viability of those products, by comparing them with the contents of their semantic lexicon for successful matches (i.e., true words). On the other hand, performance on semantically constrained trials involved generating solutions within the limits of specific semantic categories, and to evaluate the viability of those products, by comparing them with the contents of that semantic category. We reasoned that the critical contrast between unconstrained and semantically constrained trials would isolate the brain regions that are involved in generating hypotheses in unconstrained settings.

Method

Subjects

Fifteen right-handed subjects (7 females) with no history of neurological and psychiatric disorders participated in this study. All subjects were native English speakers. The mean age of the sample was 26.5 years ($SD = 3.8$), and the mean education level was 17.3 years ($SD = 2.2$). The study was approved by the Human Participants Review Sub-Committee of York University, and all subjects gave informed consent.

Materials and procedure

The stimuli (words) for this experiment were selected from verbal category norms. Verbal category norms consist of semantic categories, along with lists of exemplars (nouns) that stand in varying degrees of relationship to each semantic category. Such norms are readily available in the cognitive literature. For each semantic category (e.g., furniture), the exemplar that has the strongest relationship to it is referred to as its prototype or dominant exemplar (e.g., chair) (Rosch and Mervis, 1975). Based on the category norms reported by Battig and Montague (1969) and Uyeda and Mandler (1980), 40 semantic categories and their

respective prototypes were selected for this experiment. Semantic categories were selected based on two requirements. First, their prototypes had to be single word nouns. For example, the semantic category “A natural earth formation” was not selected because its prototype “Grand Canyon” consisted of two words (Uyeda and Mandler, 1980). Second, when the sequence of letters making up each word was altered, the letters could be rearranged back into the initial word only. We selected prototypes as opposed to any other exemplar to ensure a comparable level of consistency in the strength of category–exemplar relationships across categories. Then, the letters that made up each prototype were rearranged randomly (scrambled). This procedure resulted in the generation of 40 scrambled sequences of letters that could be rearranged to form the prototypes of 40 semantic categories.

The stimuli used in the scanner were created in two steps. First, for each semantic category (e.g., type of music) and its scrambled prototype (ZJAZ), three conditions were created. The unconstrained condition consisted of scrambled letters that could be rearranged to make a solution. The semantically constrained condition consisted of scrambled letters that could be rearranged to make a solution that belonged to a *particular semantic category*. The baseline condition consisted of scrambled letters that could be rearranged to make a *specific* word. This process resulted in the generation of 40 stimuli for each of the three conditions and thus a total of 120 stimuli. The second step was as follows: One letter at a random location was altered to another letter in half of the stimuli in each condition, such that the new sequence of letters could no longer be rearranged to form any word. In other words, 50% of the stimuli in each of the three conditions (unconstrained, semantically constrained, baseline) were insoluble. This was done to ensure that, if a subject claimed to have found a solution on each trial (i.e., pressed “yes” every time), then overall accuracy would be exactly 50% or at chance level. It was emphasized to them in advance that they were to judge each trial individually. However, more critically, this process was conducted to ensure that subjects were not presented with the same anagram sequence on consecutive trials (see Fig. 1).

In the scanner, anagrams were presented in an event-related design. The three conditions (unconstrained, semantically constrained, baseline) corresponding to each semantic category appeared in succession. The order of presentation within each semantic category was not randomized. This was done to ensure that the unconstrained condition always appeared prior to the other two conditions. However, to ensure that savings from solving any anagram problem would not be carried over automatically into the next trial, the letters that made up the anagrams on consecutive trials were made different (Fig. 1). This design strikes a balance between minimizing order effects and minimizing the likelihood of priming the solution to the unconstrained condition. There were no gaps in presentation between stimuli. Each stimulus was presented for 6 s, and subjects were instructed to indicate whether they were able to generate a solution using one of two keys (yes/no). Eight subjects used the right hand and the other seven the left hand to enter their responses to control for neural activation associated with motor control.

fMRI scanning and analysis

A 4 T Oxford Magnet Technologies magnet with a Siemens Sonata gradient coil was used to acquire T1 anatomical volume images ($1 \times 1 \times 2$ mm voxels) and twenty-two T2*-weighted

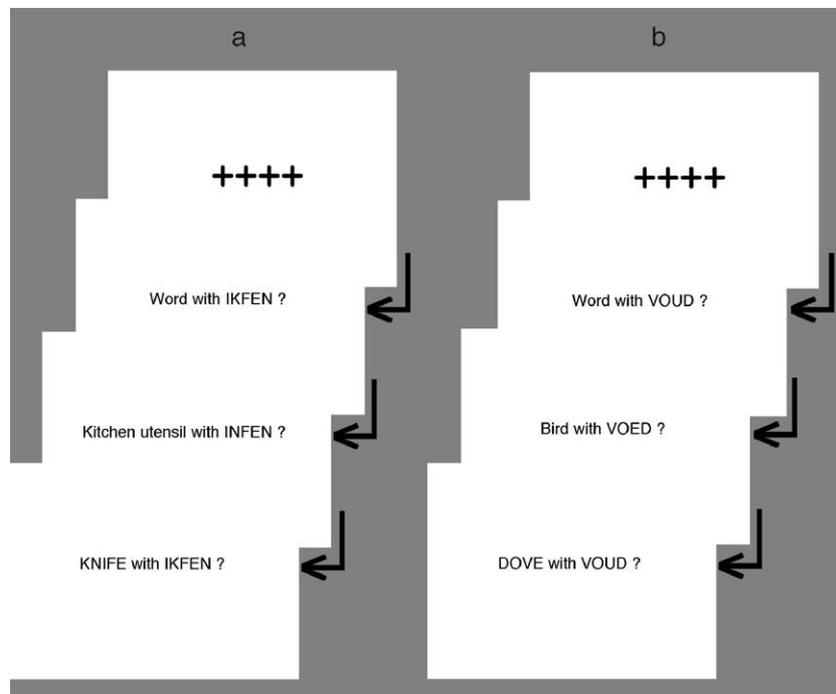


Fig. 1. Diagram represents samples of consecutive trials (unconstrained, semantically constrained, baseline) from the anagram task. A solvable–unsolvable–solvable sequence (a) and an unsolvable–solvable–unsolvable sequence (b) are shown in the diagram. The response in each case is yes/no. Duration of each trial is 6 s.

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. A total of 246 volumes were recorded during a single session, acquired with a repetition time (TR) of 3.0 s/vol. The first six volumes were discarded to allow for T1 equilibration effects (leaving 240 volumes for analysis). The stimuli were presented to subjects using a LCD projector (NEC MultiSync MT800) with a video resolution of 640×480 pixels and a light output of 370 lumens.

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 less than 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 T2* 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 $P < .05$ using a random effects model, corrected for multiple comparisons

using the False Discovery Rate (Genovese et al., 2002), and a cluster size comprised of a minimum of ten contiguous voxels. The BOLD signal was modeled as a canonical hemodynamic response function with time derivative. In addition, motor response and two covariates (number of letters in each anagram problem and response latency) were entered into the analysis but modeled as events of no interest (see Functional MRI results).

Results

Behavioral results

The average reaction time across all stimuli was 2923 ms (SD = 410). There was a significant difference in reaction time between unconstrained ($M = 3916$, SD = 513), semantically constrained ($M = 2866$, SD = 400), and baseline ($M = 1986$, SD = 316) trials, $F(2, 28) = 111$, $P < .001$. Post-hoc tests demonstrated that the difference in reaction time between any pair was significant. The average accuracy rate across all stimuli was 85%. There was a significant difference in accuracy rates between unconstrained (76%), semantically constrained (86%), and baseline (94%) conditions, $F(2, 28) = 51$, $P < .001$. Post-hoc tests demonstrated that the difference in accuracy between any pair was significant. This consistent pattern of results indicates that there was a general increase in difficulty ranging from baseline to semantically constrained to unconstrained conditions.

Functional MRI results

To test our hypothesis of right PFC involvement in unconstrained word generation, we conducted three direct categorical comparisons and one parametric analysis. The first comparison

involved unconstrained vs. baseline trials (masked inclusively with unconstrained and semantically constrained trials vs. baseline). Specifically, presentations of stimuli were treated as events. Motor response was modeled as an event of no interest. In addition, two variables were entered into the analysis as covariates and modeled as events of no interest. The first covariate was the number of letters in the prototype, which ranged from 3 to 6. This would ensure that differences in activation across trials would not be confounded by the number of letters that had to be manipulated. Second, our behavioral results demonstrated significant differences in difficulty among the three anagram trial types. Therefore, to reveal regions that distinguished unconstrained from baseline trials irrespective of difficulty, response latency was treated as a proxy measure for difficulty, entered as a covariate into the analysis, and modeled as an event of no interest. The results revealed that performance on unconstrained vs. baseline trials was associated with significant activations in right ventral lateral PFC (BA 47) (32, 36, -20, $z = 3.75$), occipital–parietal sulcus (BA 18) (2, -54, 14, $z = 4.53$; -8, -72, 32, $z = 4.39$), right insula (44, 6, 4, $z = 3.62$), left occipital gyrus (BA 19) (-38, -86, 28, $z = 3.54$), frontopolar cortex (BA 10) (8, 68, 6, $z = 3.51$), bilateral superior parietal lobe (BA 7) (-18, -50, 72, $z = 3.51$ and 24, -46, 70, $z = 3.48$), post central gyrus (BA 2) (68, -22, 32, $z = 3.29$), and cerebellum (18, -60, -24, $z = 3.42$; 30, -32, -36, $z = 3.84$) (Table 1). The reverse comparison (baseline vs. unconstrained) did not yield any significant area of activation.

The second comparison consisted of semantically constrained vs. baseline trials (masked inclusively with unconstrained and semantically constrained trials vs. baseline), conducted using the same design and covariates as the first contrast. No activation survived FDR correction ($P < .05$ using a random effects model). The reverse comparison (baseline vs. semantically constrained) did not reveal any significant area of activation either.

The third comparison involving a direct contrast between unconstrained versus semantically constrained trials (masked inclusively with unconstrained and semantically constrained trials vs. baseline), conducted using the same design and covariates as the first contrast, revealed significant activations in right ventral lateral PFC (BA 47) (34, 34, -24, $z = 3.71$), right superior parietal lobe (BA 7) (30, -44, 70, $z = 4.25$), occipital–parietal sulcus (BA

18) (0, -52, 20, $z = 4.62$; -2, -76, 30, $z = 4.46$), frontopolar cortex (BA 10) (4, 68, 2, $z = 4.49$), left superior frontal gyrus (BA 8) (-22, 36, 42, $z = 3.98$; -22, 42, 40, $z = 3.86$), right post central gyrus (BA 4) (32, -22, 68, $z = 4.85$; 68, -22, 32, $z = 3.40$), and cerebellum (28, -38, -34, $z = 3.96$) (Table 2 and Fig. 2). Next, we repeated this analysis based on accurate responses only. The results demonstrated a similar pattern of significant activations in right ventral lateral PFC (BA 47) (36, 34, -24, $z = 3.11$), occipital–parietal sulcus (BA 18) (2, -50, 18, $z = 4.58$), frontopolar cortex (BA 10) (4, 68, 2, $z = 4.60$), left superior frontal gyrus (BA 8) (-20, 38, 42, $z = 3.45$), right post central gyrus (BA 4) (32, -22, 68, $z = 4.25$; 68, -22, 32, $z = 3.61$), and cerebellum (26, -40, -38, $z = 3.44$). The reverse comparison (semantically constrained vs. unconstrained) did not yield any significant area of activation.

To reveal regions where activation covaried as a function of varying constraints, we conducted a parametric analysis of fMRI data. Specifically, presentations of anagram problems were treated as events, coupled with the level of constraint (unconstrained = 3, semantically constrained = 2, baseline = 1) as the parameter of interest. As before, motor response and two covariates (number of letters in each anagram problem and response latency) were entered into the analysis and treated as events of no interest. Although no activation survived FDR correction ($P < .05$ using a random effects model), there was activation at an uncorrected level ($P < .005$) in right ventral lateral PFC (BA 47) (30, 34, -20, $z = 2.58$) (Fig. 2).

Finally, we conducted an additional analysis aimed specifically at highlighting brain areas that are affected by task difficulty. Recall that in all analyses reaction time was treated as a proxy measure for difficulty. Therefore, we carried out a parametric analysis where presentations of slides were treated as events, coupled with reaction time as the parameter of interest. Although no activation survived FDR correction ($P < .05$ using a random effects model), the results demonstrated that activation in right inferior temporal gyrus (BA 20) (32, -26, -34, $z = 3.77$), anterior medial prefrontal cortex (BA 9) (6, 66, 30, $z = 3.45$), nucleus accumbens (-8, 10, -14, $z = 3.40$), anterior medial prefrontal cortex (BA 10) (2, 70, 0, $z = 3.29$), and posterior cingulate (BA 29) (-4, -48, 18, $z = 3.20$) covaried in relation to reaction time. Critically, there was no activation in right ventral lateral PFC (BA 47).

Table 1

Activation results of unconstrained anagram vs. baseline trials (masked inclusively with all conditions versus baseline)

Region of activation	BA	L	Z	x	y	z
Occipital–parietal sulcus	18	-	4.53	2	-54	14
	18	L	4.39	-8	-72	32
Ventral lateral PFC	47	R	3.75	32	36	-20
Insula	-	R	3.62	44	6	4
Occipital gyrus	19	L	3.54	-38	-86	28
Frontopolar cortex	10	R	3.51	8	68	6
Superior parietal lobe	7	L	3.51	-18	-50	72
	7	R	3.48	24	-46	70
Cerebellum	-	R	3.42	18	-60	-24
	-	R	3.84	30	-32	-36
Post central gyrus	2	R	3.29	68	-22	32

Note. The reverse comparison (baseline-unconstrained) did not result in any significant area of activation. Regions are designated using the MNI coordinates. BA indicates Brodmann area. L indicates laterality. Z indicates z score.

Discussion

This study manipulated constraints on the problem space of an anagram task to identify the brain regions that are involved in generating hypotheses in unconstrained settings. Three conditions, corresponding to three levels of constraints on the transformation function, and thus the size of the solution space, were used. The key comparison of unconstrained vs. semantically constrained trials revealed activations in several areas including the predicted right ventral lateral PFC (BA 47), as well as right superior parietal lobe (BA 7), occipital–parietal sulcus (BA 18), frontopolar cortex (BA 10), left superior frontal gyrus (BA 8), right post central gyrus (BA 4), and cerebellum (Table 2). We argue that these activations reflect different processing demands that the absence of solution constraints places on anagram solution, including hypothesis generation, semantic retrieval, semantic categorization, and cognitive monitoring.

Table 2

Activation results of unconstrained vs. semantically constrained anagram trials (masked inclusively with all conditions versus baseline)

Region of activation	BA	L	Z	x	y	z
Post central gyrus	4	R	4.85	32	-22	68
	4	R	3.40	68	-22	32
Superior parietal lobe	7	R	4.25	30	-44	70
Occipital–parietal sulcus	18	-	4.62	0	-52	20
	18	-	4.46	-2	-76	30
Frontopolar cortex	10	R	4.49	4	68	2
Superior frontal gyrus	8	L	3.98	-22	36	42
	8	L	3.86	-22	42	40
Cerebellum	-	R	3.96	28	-38	-34
Ventral lateral PFC	47	R	3.71	34	34	-24

Note. The reverse comparison (semantically constrained–unconstrained) did not result in any significant area of activation. Regions are designated using the MNI coordinates. BA indicates Brodmann area. L indicates laterality. Z indicates z score.

One requirement for solving anagram problems is the ability to determine whether generated solutions are words or non-words. This requires a process of semantic retrieval and evaluation to compare potential solutions to the semantic lexicon. The provision of cues to facilitate semantic retrieval improves performance on anagram problems (Dominowski and Ekstrand, 1967; Greeno, 1978; Maltzman and Morrisett, 1952; Mendelsohn et al., 1966; Rees and Israel, 1935). The search space for semantic retrieval is much larger in the unconstrained trials than the semantically constrained trials. Activations in right post central gyrus (BA 4), right superior parietal lobe (BA 7), occipital–parietal sulcus (BA 18), and cerebellum may well reflect this different processing demand (Henke et al., 2003; Köhler et al., 1998; for review, see Cabeza and Nyberg, 2000). It is noteworthy that activation in the above structures did not distinguish semantically constrained from baseline trials. This may be because imposing limits on the search space and limiting retrieval to a single semantic category (in semantically constrained trials) may have resulted in a much lower

demand on semantic retrieval than was the case in the unconstrained trials. In addition, there is some evidence to suggest that activation in left superior frontal gyrus (BA 8) in the unconstrained vs. semantically constrained contrast may be due to its increased engagement in evaluating the products of the generative process (semantic categorization) (Grossman et al., 2002). One would expect this evaluative process to also distinguish unconstrained from baseline trials. Indeed, the left superior frontal gyrus (BA 8) (-20, 34, 46, $z = 3.04$) was also activated in that contrast, but this activation did not survive FDR correction ($P < .05$ using a random effects model).

Successful completion of anagram problems also requires updating of partial solutions as the problem solver discards unsuccessful hypotheses for better ones (Greeno, 1978). One would expect the demand on such monitoring processes to be higher in unconstrained than semantically constrained trials because of the larger search space in the former condition. This increased demand for cognitive monitoring may account for the activation observed in the frontopolar cortex (BA 10) in both unconstrained vs. semantically constrained and unconstrained vs. baseline trials. Previous studies have implicated the frontal pole (BA 10) in tasks that require updating of partial information and cognitive monitoring (Braver and Bongiolatti, 2002; Fletcher and Henson, 2001; Koechlin et al., 1999). However, there is also recent evidence from research on prospective memory to suggest that there may be a finer grained dissociation between the functions of the medial and lateral BA 10 (Burgess et al., 2003). Briefly, prospective memory tasks involve maintaining intention in memory for delayed execution. Evidence suggests that medial BA 10 may be involved in suppressing attention from external (i.e., ongoing) stimuli, whereas lateral BA 10 may be involved in maintaining attention on internally generated cognitions. Because the area activated in our study was medial BA 10 (4, 68, 2), it is possible that in the context of cognitive monitoring its particular function may have been the withdrawal of attention from irrelevant cues such as discarded unsuccessful hypotheses.

However, our main interest in this study is the response of the right PFC to the absence of constraints on the search space.

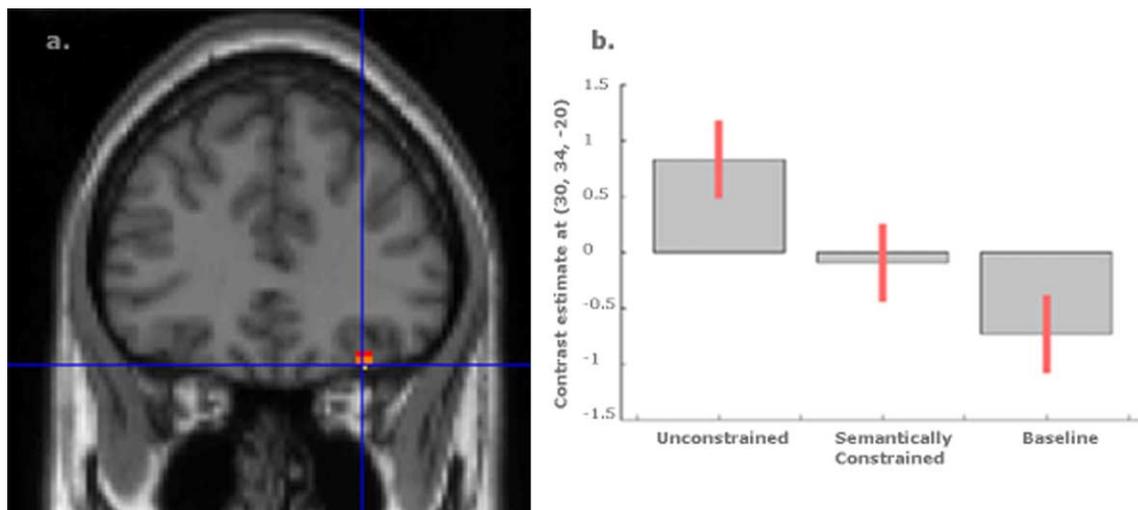


Fig. 2. (a) Hypothesis generation in unconstrained anagram trials is associated with significant activation in right ventral lateral PFC (BA 47) (32, 34, -22, $z = 3.35$). The activated cluster is comprised of 12 contiguous voxels. SPM rendered into standard stereotactic space and superimposed on to coronal MRI in standard space. Region is designated using MNI coordinates. (b) Condition specific parameter estimates demonstrate that activation in right ventral lateral PFC (30, 34, -20) increases as a function of decreasing constraints on the problem space in the anagram task.

Activation in right ventral lateral PFC distinguished not only unconstrained trials from semantically constrained trials, but also unconstrained trials from baseline trials. It can be argued that the difference between the unconstrained condition and baseline condition was one of (open-ended) generation and evaluation cycles (in the unconstrained condition) vs. only evaluation of a given end state (in the constrained condition), thus confounding the issue of hypothesis generation with the issue of constraints. However, in our critical comparison of unconstrained vs. semantically constrained trials, both trial types involved generate-and-evaluate cycles and are therefore distinguished only by the level of constraints. A parametric analysis showed that activation in right ventral lateral PFC covaried with the level of constraints (Fig. 2). Furthermore, activation in right ventral lateral PFC did not covary with problem difficulty as measured by reaction time. Collectively, these results provide evidence that the involvement of right ventral lateral PFC in anagram problems is specifically a function of the level of constraints on the generation task.

Although activation in right ventral lateral PFC has been associated with spatial attention (e.g., Awh and Jonides, 1998) and working memory (e.g., D'Esposito et al., 1998; Owen, 1997; Petrides, 1994), it is unlikely that either of these processes can account for the involvement of right ventral lateral PFC (BA 47) in the unconstrained versus semantically constrained contrast. First, although anagrams have a spatial component, there is no reason to believe that spatial demands would vary across the three trial types. Second, while one could argue that the unconstrained condition places higher demands on working memory because of the requirement to generate *more* hypotheses in that condition, much evidence from imaging studies indicates that it is right dorsal lateral PFC (BA 46) rather than right ventral lateral PFC (BA 47) that mediates variations in cognitive load across both verbal and spatial modalities (Barch et al., 1997; Bechara et al., 1998; Braver et al., 2001; Cohen et al., 1997; Goel and Vartanian, *in press*; Leung et al., 2002; Thomas et al., 1999; Zurowski et al., 2002).

We interpret the activation in right ventral lateral PFC (BA 47) in terms of its role in hypothesis generation in unconstrained conditions. Not only is this interpretation consistent with the lesion data (Burgess, 2000; Goel and Grafman, 2000), but also with several neuroimaging studies that have employed tasks containing hypotheses generation components. For example, Desmond et al. (1998) presented subjects with a word stem completion task where some word stems could be completed in many possible ways (easy trials) and others that could be completed in only a few ways (hard trials). The authors argued that on easy trials subjects would easily generate many satisfactory solutions and would simply select one from the generated set, whereas on hard trials they would have to engage in sustained search to generate a possible solution. A comparison of hard versus easy trials revealed significant activation in largely a right cerebellar system and the right inferior PFC (BA 47; 30, 25, -5), suggesting its involvement increases with difficulty of response generation.

The involvement of right PFC in harder vs. easier generate-and-evaluate cycles is perhaps more clearly illustrated in a study by Goel and Dolan (2000) that presented subjects with drawings of triplets of novel (unknown) animals and asked them to classify all members of the triplet as belonging to the same species. This condition of the task required subjects to generate and evaluate (multiple) hypotheses, while another condition required subjects to evaluate a given hypothesis. The tasks varied in difficulty along an orthogonal dimension. The main finding was a task by difficulty

interaction whereby the difference between hard hypothesis generation and evaluation vs. hard hypothesis evaluation resulted in greater activation in right inferior PFC (BA 47; 34, 28, -2 and 38, 40, -14) than the difference between easy hypothesis generation and evaluation vs. easy hypothesis evaluation.

What these studies have in common with our task is that their hard conditions involve relatively less constrained solution search. In the Desmond et al. (1998) study, word stems in the easy trials would automatically activate word patterns, whereas in the hard trials no such patterns would be activated, requiring an unfacilitated search. Similarly, in the Goel and Dolan (2000) study, the images in the easy trials would be sorted into recognizable patterns, whereas in the hard trials a great deal of uncertainty existed about the patterns, requiring an unfacilitated search. Our results – by using difficulty as a covariate in the analysis – demonstrate more clearly that what was driving right PFC activation in these studies was not simply increased difficulty, but the lack of constraints in the difficult conditions.

It is also noteworthy that the present study, along with Desmond et al. (1998), employed linguistic stimuli, while the task used by Goel and Dolan (2000) employed spatial stimuli. This suggests that the involvement of right ventral lateral BA 47 is task specific and reinforces recent claims that hemispheric asymmetry is a function of task rather than modality (Stephan et al., 2003).

In conclusion, this study was conducted to identify the brain regions that are involved in generating solutions in an anagram task as constraints on the solution space are manipulated. As per our a priori hypothesis, the critical comparison of unconstrained vs. semantically constrained trials revealed significant activation in right ventral lateral PFC (BA 47), despite the linguistic nature of the stimuli. This study extends the findings from the lesion studies by demonstrating that the lack of discernible patterns to constrain and guide solution search is sufficient to engage right *ventral lateral* PFC in hypothesis generation tasks.

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References

- Ashburner, J., Friston, K.J., 1999. Nonlinear spatial normalization using basis functions. *Hum. Brain Mapp.* 7 (4), 254–266.
- Awh, E., Jonides, J., 1998. Spatial selective attention and spatial working memory. In: Parasuraman, R. (Ed.), *The Attentive Brain*. M.I.T. Press, Cambridge, MA, pp. 353–380.
- Barch, D.M., Braver, T.S., Nystrom, L.E., Forman, S.D., Noll, D.C., Cohen, J.D., 1997. Dissociating working memory from task difficulty in human prefrontal cortex. *Neuropsychologia* 35 (10), 1373–1380.
- Battig, W.F., Montague, W.E., 1969. Category norms for verbal items in 56 categories: a replication and extension of the Connecticut Category Norms. *J. Exp. Psychol. Monogr.* 80 (3 Pt. 2).
- Bechara, A., Damasio, H., Tranel, D., Anderson, S.W., 1998. Dissociation of working memory from decision making within the human prefrontal cortex. *J. Neurosci.* 18, 428–437.
- Braver, T.S., Bongiolatti, S., 2002. The role of frontopolar cortex in subgoal processing during working memory. *NeuroImage* 15, 523–536.
- Braver, T.S., Barch, D.M., Kelley, W.M., Buckner, R.L., Cohen, N.J., Miezin, F.M., Snyder, A.Z., Ollinger, J.M., Akbudak, E., Conturo, T.E., Petersen, S.E., 2001. Direct comparison of prefrontal cortex regions

- engaged by working and long-term memory tasks. *NeuroImage* 14 (1 Pt. 1), 48–59.
- Burgess, P.W., 2000. Strategy application disorder: the role of the frontal lobes in human multitasking. *Psychol. Res.* 63 (3–4), 279–288.
- Burgess, P.W., Veitch, E., de Lacy Costello, A., Shallice, T., 2000. The cognitive and neuroanatomical correlates of multitasking. *Neuropsychologia* 38, 848–863.
- Burgess, P.W., Scott, S.K., Frith, C.D., 2003. The role of the rostral frontal cortex (area 10) in prospective memory: a lateral versus medial dissociation. *Neuropsychologia* 41, 906–918.
- Cabeza, R., Nyberg, L., 2000. Imaging cognition II: an empirical review of 275 PET and fMRI studies. *J. Cogn. Neurosci.* 12, 1–47.
- Cohen, J.D., Perlstein, W.M., Braver, T.S., Nystrom, L.E., Noll, D.C., Jonides, J., Smith, E.E., 1997. Temporal dynamics of brain activation during a working memory task. *Nature* 386 (6625), 604–608.
- D’Esposito, M., Aguirre, G.K., Zarahn, E., Ballard, D., Shin, R.K., Lease, J., 1998. Functional MRI studies of spatial and nonspatial working memory. *Cogn. Brain Res.* 7, 1–13.
- Desmond, J.E., Gabrieli, J.D., Glover, G.H., 1998. Dissociation of frontal and cerebellar activity in a cognitive task: evidence for a distinction between selection and search. *NeuroImage* 7 (4 Pt. 1), 368–376.
- Dominowski, R.L., 1969. The effect of pronunciation practice on anagram difficulty. *Psychon. Sci.* 16, 99–100.
- Dominowski, R.L., Ekstrand, B.R., 1967. Direct and associative priming in anagram solving. *J. Exp. Psychol.* 74, 84–86.
- Eslinger, P.J., Damasio, A.R., 1985. Severe disturbance of higher cognition after bilateral frontal lobe ablation: patient EVR. *Neurology* 35, 1731–1741.
- Evans, A.C., Collins, D.L., Mills, S.R., Brown, E.D., Kelly, R.L., Peters, T.M., 1993. 3D statistical neuroanatomical models from 305 MRI volumes. *Proc. IEEE-Nucl. Sci. Symp. Med. Imaging*, 1813–1817.
- Fletcher, P.C., Henson, R.N.A., 2001. Frontal lobes and human memory: insights from functional neuroimaging. *Brain* 124, 849–881.
- 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 approach. *Hum. Brain Mapp.* 2, 189–210.
- Gavurin, E.I., 1967a. Anagram solution and spatial aptitude. *J. Psychol.* 65, 65–68.
- Gavurin, E.I., 1967b. Anagram solving under conditions of letter order randomization. *J. Psychol.* 65, 179–182.
- Genovese, C.R., Lazar, N.A., Nichols, T., 2002. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *NeuroImage* 15, 870–878.
- Goel, V., 1995. *Sketches of Thought*. MIT Press, Cambridge, MA.
- Goel, V., 2002. Planning: neural and psychological. In: Nadel, L. (Ed.), *Encyclopedia of Cognitive Science*, vol. 3. Macmillan, NY, pp. 697–703.
- Goel, V., Dolan, R.J., 2000. Anatomical segregation of component processes in an inductive inference task. *J. Cogn. Neurosci.* 12 (1), 1–10.
- Goel, V., Grafman, J., 2000. The role of the right prefrontal cortex in ill-structured problem solving. *Cogn. Neuropsychol.* 17 (5), 415–436.
- Goel, V., Grafman, J., Tajik, J., Gana, S., Danto, D., 1997. A study of the performance of patients with frontal lobe lesions in a financial planning task. *Brain* 120, 1805–1822.
- Goel, V., Vartanian, O., in press. Dissociating the roles of right ventral lateral and dorsal lateral prefrontal cortex in generation and maintenance of hypotheses in set shift problems. *Cereb. Cortex*.
- Goldberg, E., Podell, K., Lovell, M., 1994. Lateralization of frontal lobe functions and cognitive novelty. *J. Neuropsychiatry* 6, 371–378.
- Greeno, J.G., 1978. Natures of problem solving abilities. In: Estes, W.K. (Ed.), *Handbook of Learning and Cognitive Processes*, vol. 5. John Wiley and Sons, New York, pp. 239–270.
- Grossman, M., Smith, E.E., Koenig, P., Glosser, G., DeVita, C., Moore, P., McMillan, C., 2002. The neural basis for categorization in semantic memory. *NeuroImage* 17, 1549–1561.
- Henke, K., Mondadori, C.R.A., Treyer, V., Nitsch, R.M., Buck, A., Hock, C., 2003. Nonconscious formation and reactivation of semantic associations by way of the medial temporal lobe. *Neuropsychologia* 41, 863–876.
- Koechlin, E., Basso, G., Pietrini, P., Panzer, S., Grafman, J., 1999. The role of the anterior prefrontal cortex in human cognition. *Nature* 399, 148–151.
- Köhler, S., McIntosh, A.R., Moscovitch, M., Winocur, G., 1998. Functional interactions between medial temporal lobes and posterior neocortex related to episodic memory retrieval. *Cereb. Cortex* 8, 451–461.
- 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. *J. Cogn. Neurosci.* 14 (4), 659–671.
- Maltzman, I., Morrisett, L., 1952. Different strengths of set in the solution of anagrams. *J. Exp. Psychol.* 44, 242–246.
- Mendelsohn, G.A., Griswold, B.B., Anderson, M.L., 1966. Individual differences in anagram solving ability. *Psychol. Rep.* 19, 429–439.
- Metcalfe, J., 1986. Premonitions of insight predict impending error. *J. Exper. Psychol., Learn., Mem., Cogn.* 12, 623–634.
- Newell, A., Simon, H.A., 1972. *Human Problem Solving*. Prentice-Hall, Englewood Cliffs, NJ.
- Novick, L.R., Sherman, S.J., 2003. On the nature of insight solutions: evidence from skill differences in anagram solution. *Q. J. Exp. Psychol.* 56A, 351–382.
- Owen, 1997. The functional organization of working memory processes within human lateral frontal cortex: the contribution of functional neuroimaging. *Eur. J. Neurosci.* 9, 1329–1339.
- Petrides, L., 1994. Frontal lobes and behaviour. *Curr. Opin. Neurobiol.* 4, 207–211.
- Rees, H., Israel, H., 1935. An investigation of the establishment and operation of mental sets. *Psychol. Monogr.* 46 (Whole No. 210).
- Reitman, W.R., 1964. Heuristic decision procedures, open constraints, and the structure of ill-defined problems. In: Shelly, W.M., Bryan, G.L. (Eds.), *Human Judgements and Optimality*. John Wiley and Sons, New York, pp. 282–315.
- Rosch, E., Mervis, C.B., 1975. Family resemblances: studies in the internal structure of categories. *Cogn. Psychol.* 7, 573–605.
- Ronning, R.R., 1965. Anagram solution times: a function of the “ruleout” factor. *J. Exp. Psychol.* 69, 35–39.
- Shallice, T., Burgess, P.W., 1991. Deficits in strategy application following frontal lobe damage in man. *Brain* 114, 727–741.
- Simon, H.A., 1973. The structure of ill structured problems. *Artif. Intell.* 4, 181–201.
- Stephan, K.E., Marshall, J.C., Friston, K.J., Rowe, J.B., Ritzl, A., Zilles, K., Fink, G.R., 2003. Lateralized cognitive processes and lateralized task control in the human brain. *Science* 301 (5631), 384–386.
- Thomas, K.M., King, S.W., Franzen, P.L., Welsh, T.F., Berkowitz, A.L., Noll, D.C., Birmaher, V., Casey, B.J., 1999. A developmental functional MRI study of spatial working memory. *NeuroImage* 10 (3 Pt. 1), 327–338.
- Uyeda, K.M., Mandler, G., 1980. Prototypicality norms for 28 semantic categories. *Behav. Res. Meth. Instrum.* 12, 587–595.
- Weisberg, R.W., Alba, J.W., 1981. An examination of the alleged role of “fixation” in the solution of several “insight” problems. *J. Exp. Psychol.: General* 110, 169–192.
- Worsley, K.J., Friston, K.J., 1995. Analysis of fMRI time-series revisited—again. *NeuroImage* 2, 173–181.
- Zurowski, B., Gostomzyk, J., Gron, G., Weller, R., Schirmeister, H., Neumeier, B., Spitzer, M., Reske, S.N., Walter, H., 2002. Dissociating a common working memory network from different neural substrates of phonological and spatial stimulus processing. *NeuroImage* 15 (1), 45–57.