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Research Report

Prefrontal organization of cognitive control according to levels of abstraction

Kalina Christoff^{a,b,*}, Kamyar Keramatian^b, Alan M. Gordon^c,
Rachelle Smith^a, Burkhard Mädler^{d,e}

^aDepartment of Psychology, University of British Columbia, Vancouver, BC, Canada V6T 1Z4

^bProgram in Neuroscience, University of British Columbia, Vancouver, BC, Canada V6T 1Z4

^cDepartment of Psychology, Stanford University, CA 94305, USA

^dDepartment of Physics and Astronomy, University of British Columbia, Vancouver, BC, Canada V6T 1Z4

^ePhilips Healthcare, Markham, ON, Canada L6C 2S3

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ABSTRACT

The prefrontal cortex (PFC) plays a crucial role in cognitive control and higher mental functions by maintaining working memory representations of currently relevant information, thereby inducing a mindset that facilitates the processing of such information. Using fMRI, we examined how the human PFC implements mindsets for information at varying levels of abstraction. Subjects solved anagrams grouped into three kinds of blocks (concrete, moderately abstract, and highly abstract) according to the degree of abstraction of their solutions. Mindsets were induced by cuing subjects at the beginning of every block as to the degree of abstraction of solutions they should look for. Different levels of abstraction were matched for accuracy and reaction time, allowing us to examine the effects of varying abstraction in the absence of variations in cognitive complexity. Mindsets for concrete, moderately abstract, and highly abstract information were associated with stronger relative recruitment of ventrolateral, dorsolateral, and rostrolateral PFC regions, respectively, suggesting a functional topography whereby increasingly anterior regions are preferentially associated with representations of increasing abstraction. Rather than being a structural property of the neurons in different prefrontal subregions, this relative specialization may reflect one of the principles according to which lateral PFC adaptively codes and organizes task-relevant information.

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1. Introduction

The prefrontal cortex (PFC) plays a central role in abstract thought (Goldstein, 1944; Luria, 1966) and higher mental functions (Shallice, 1988; Duncan et al., 1995; Duncan et al., 1996) by maintaining on-line representations of currently

relevant information (Fuster, 1980; Cohen et al., 1990; Miller and Cohen, 2001; Everling et al., 2002). The PFC has been implicated in maintaining information at varying degrees of abstraction: from concrete information such as specific objects and perceptual features (e.g., Fuster, 1980; Goldman-Rakic, 1987), to abstract rules about the relationship between

* Corresponding author. Department of Psychology, University of British Columbia, 2136 West Mall, Vancouver, BC, V6T 1Z4 Canada. Fax: +1 604 822 6923.

E-mail address: kchristoff@psych.ubc.ca (K. Christoff).

URL: <http://www.christofflab.ca> (K. Christoff).

objects (e.g., “same” vs. “different”, see Wallis et al., 2001), to highly abstract task contexts that are themselves comprised of multiple abstract rules (Cohen et al., 1990; O’Reilly et al., 2002; Koehlin et al., 2003; Sakai and Passingham, 2003).

Research in non-human primates (Dias et al., 1996, 1997) has suggested that different prefrontal regions may support information at varying levels of abstraction (O’Reilly et al., 2002; Rougier et al., 2005; Botvinick, 2007), with dorsal PFC supporting abstract dimensional representations and orbito-frontal PFC supporting concrete featural representations. Consistent with this, recent patient findings indicate that anterior PFC lesions impair performance on more abstract tasks, whereas posterior PFC lesions impair more concrete tasks (Badre et al., 2009). Adding to these results, human neuroimaging studies have implicated the most anterior part of the lateral PFC, also known as rostralateral PFC (RLPFC), in supporting representations at some of the highest levels of abstraction, while associating less abstract representations with more posterior PFC regions such as the dorsolateral (DLPFC) and ventrolateral (VLPFC) (Christoff et al., 2003; Koehlin et al., 2003; Sakai and Passingham, 2003; Bunge et al., 2005; Badre and D’Esposito, 2007; Smith et al., 2007; Wendelken et al., 2008). Based on these findings, it has recently been proposed that the human lateral PFC may be organized according to at least three levels of representational abstraction, with increasing abstraction recruiting increasingly anterior regions (Fig. 1) (Christoff, 2003; Bunge and Zelazo, 2006; Badre and D’Esposito, 2007; Christoff and Keramatian, 2007).

One of the greatest challenges in testing any model of prefrontal organization proposing a posterior-to-anterior functional gradient is the confound of task difficulty. Task difficulty relates to the amount of cognitive effort involved in solving a particular task (Barch et al., 1997; Duncan et al., 2000) and is empirically measured in terms of performance indexes such as reaction time and accuracy (e.g., Demb et al., 1995; Barch et al., 1997; Bor et al., 2003). In general, tasks that are associated with relatively low task difficulty typically recruit

posterior PFC regions. As task difficulty increases, however, PFC recruitment spreads in an increasingly anterior direction to include first DLPFC and then RLPFC (e.g., Baker et al., 1996; Braver et al., 1997; Smith and Jonides, 1997; D’Esposito et al., 1999; Rypma et al., 1999; Christoff et al., 2001; Kroger et al., 2002; van den Heuvel et al., 2003). An association between increased task difficulty and lateral PFC recruitment is found consistently across a wide range of cognitive domains (Duncan and Owen, 2000). Several theories of prefrontal functions have proposed a hierarchical posterior-to-anterior mapping of cognitive control processes (Fuster, 1980; Christoff and Gabrieli, 2000; Koehlin et al., 2003; Badre and D’Esposito, 2007), in which each superordinate control process and its associated PFC subregion re-represents subordinate processes and their associated PFC subregions (Goldberg and Bilder, 1987). Task difficulty, however, remains a recurrent issue in experimental tests of these theories, as well as a frequent confound in measures of abstraction (Christoff and Keramatian, 2007).

The present study was designed to allow us to test the hypothesis that different regions of lateral PFC are preferentially involved in cognitive control at different levels of abstraction, while at the same time controlling for task difficulty. Based on findings from human and non-human primates, we expected that VLPFC would be associated with cognitive control processes geared towards concrete representations; DLPFC, with moderately abstract representations; and RLPFC, with highly abstract representations (Fig. 1). This topography was hypothesized to hold in both hemispheres, consistent with previous findings (Deglin and Kinsbourne, 1996; Goel and Dolan, 2001; Binder et al., 2005; Allen et al., 2007; Studer and Hubner, 2008) demonstrating that the processing of abstract and concrete information is either bilaterally distributed or lateralized to either hemisphere in a task dependent manner.

To address the issue of task difficulty, we chose a form of cognitive control that involves implementing a mindset, or a goal-driven state that achieves “cognitive tuning” towards task-congruous information (Gollwitzer, 1990). In contrast to other paradigms where cognitive control is organized hierarchically according to the level of task embeddedness, the implementation of mindsets allowed us to modulate representational abstraction while keeping task difficulty constant. Importantly, we did not explicitly manipulate task difficulty. Other studies have already demonstrated a dissociation between task difficulty and cognitive processing in the PFC (Barch et al., 1997; Bor et al., 2003). Accordingly, the goal of the present experiment was not to provide a demonstration of such dissociation but instead to provide a test of the levels of abstraction hypotheses in the absence of variation in task difficulty.

To induce mindsets at varying level of abstraction, we used an anagram solution task (Fig. 2). Mindsets can be effectively induced during anagram tasks by presenting solution-related categorical cues that have been shown to facilitate the solution process (Schuberth et al., 1979; Richardson and Johnson, 1980; Seidenstadt, 1982). When anagrams are presented in groups of semantically related blocks (Safren, 1962; Dominowski and Ekstrand, 1967), the process of solution is thought to be facilitated by limiting the search space of possible solutions (Greeno, 1978).

The present study used this behavioral phenomenon of category-cue presentation to elicit a mindset for solutions at a

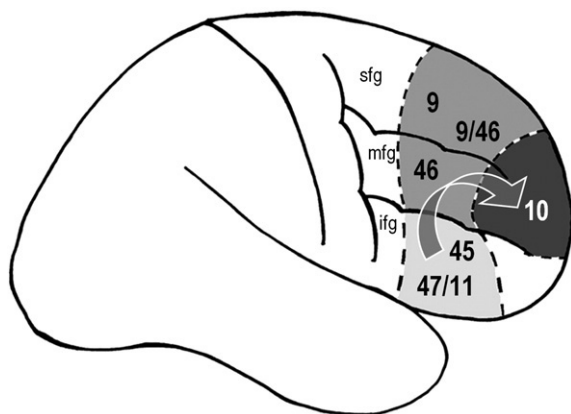


Fig. 1 – Subregions of the lateral prefrontal cortex: The ventrolateral prefrontal cortex (VLPFC, BA 45, 47, and 47/11), the dorsolateral prefrontal cortex (DLPFC; BA 46, 9/46, and 9), and the rostralateral prefrontal cortex (RLPFC, BA 10). The arrow indicates direction of increase in representational abstraction. Abbreviations: ifg, inferior frontal gyrus; mfg, middle frontal gyrus; sfg, superior frontal gyrus.

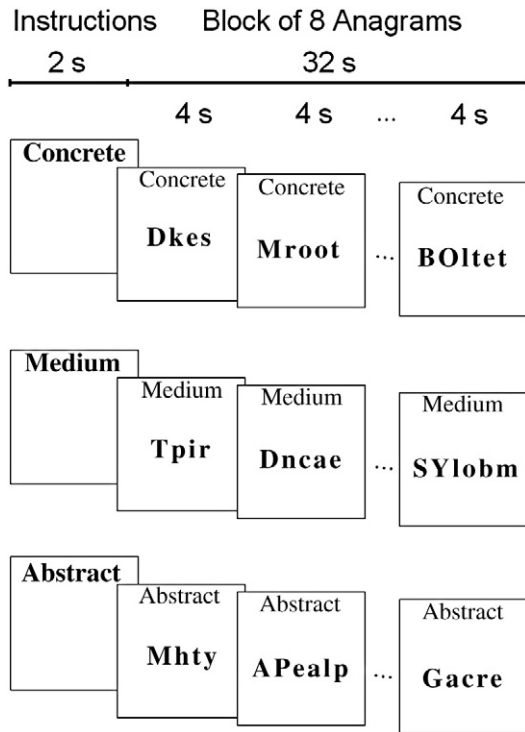


Fig. 2 – Anagrams task design and different anagram conditions. Each block was 34 s long and began with a 2 s period of instructions, during which a cue was presented indicating the level of abstraction of anagram solutions in that block. The words “concrete”, “medium”, and “abstract” were used as cues for the concrete, moderately abstract, and highly abstract anagrams conditions, respectively. To facilitate the process of reaching a solution, either the first letter (for 4- and 5-letter words) or the first two letters (for 6- and 7-letter words) of each anagram were fixed in the correct positions, indicated by capitalization (e.g. “H r m a” and “L E r t e t”).

particular level of abstraction. In addition, we took advantage of the fact that previous neuroimaging research (Vartanian and Goel, 2005) has already established the validity of using category-cues during anagram solution in the fMRI scanner. In the present study, subjects solved blocks of anagrams grouped according to the level of abstraction of their solutions. All solution words were nouns selected from the MRC psycholinguistics database (Wilson, 1988), with abstraction ratings according to Paivio et al. (1968). Each anagram had only one solution. Three kinds of blocks were used; i) blocks of anagrams with concrete solutions (e.g., “desk”, “motor”) ii) blocks of anagrams with moderately abstract solutions (e.g., “trip”, “dance”) and iii) blocks of anagrams with highly abstract solutions (e.g., “myth”, “appeal”).

During each block, subjects saw a cue indicating the level of abstraction of solution words. This cue was the word “abstract” for the highly abstract blocks of anagrams, “medium” for the moderately abstract blocks, and “concrete” for the concrete blocks (Fig. 2). The cue helped evoke a mindset (Dominowski and Ekstrand, 1967) at one of three levels of

abstraction. Subjects received extensive instructions and examples of words at each level of abstraction in order to ensure that they had a good understanding of the different abstraction categories. A behavioral pilot study was conducted to ensure that anagram conditions were matched for accuracy and reaction time.

2. Results

2.1. Behavioral results

Reaction time and accuracy during the fMRI study were closely matched across the different levels of abstraction (Fig. 3). Mean accuracy for highly abstract anagrams was 53.2% (SD=15.6%, range=27.1%–81.2%); for moderately abstract anagrams 52.7% (SD=14.2%, range=36.5%–83.3%); and for concrete anagrams 53.1% (SD=14.3%, range=37.5%–84.4%). Accuracy did not differ significantly across conditions as indicated by a repeated-measures ANOVA ($F_{2,30}=0.09, P>0.05$). Effect sizes (Cohen’s *d*) for the three pair-wise comparisons were <0.034 .

The average response time for correct responses was 1380.3 ms (SD=231.5 ms), 1405.3 ms (SD=227.7 ms), and 1407.4 ms (SD=292.4 ms) for the highly abstract, moderately abstract, and concrete conditions, respectively, with no significant differences across conditions ($F_{2,30}=0.73, P>0.05$) and effect sizes (Cohen’s *d*) for the three pair-wise comparisons <0.109 .

2.2. Head motion

Since subjects produced their responses verbally, it was important to ensure that this did not result in larger than normal or task-correlated head motion that could adversely affect the results. Results indicated that motion estimates for all 16 subjects included in the analysis were within the range of those normally observed in fMRI studies (less than 3 mm in translation estimates). The absolute motion translation estimates ranged between 0.26 and 1.48 mm ($M=0.71, SD=0.34$) in the x direction; 0.30 to 1.97 mm ($M=0.87, SD=0.56$) in the y direction; and 0.63 to 2.71 mm ($M=1.57, SD=0.72$) in the z

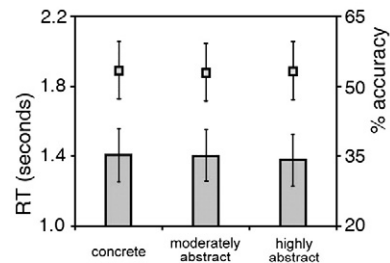


Fig. 3 – Behavioral performance. Difficulty (reaction time and accuracy) was closely matched and did not differ significantly across conditions. Bar-graphs at the lower part of the figure indicate mean reaction times; squares at the top part of figure indicate mean accuracy across conditions. Black bars at each mean indicate its standard error.

direction. Task-correlated motion with respect to the motion estimates and their linear combinations was also low ($r < 0.14$).

2.3. fMRI results

To test the hypothesis that different prefrontal regions would show increased relative recruitment at different levels of abstraction, each condition was compared to the average of the other two conditions, resulting in three comparisons of interest. The observed activations (Fig. 4 and Table 1) revealed specific prefrontal subregions associated with each level of abstraction. Activation in left VLPFC (BA 47/11) (Fig. 4a) was observed when the concrete mindset condition was compared to the other two conditions (peak $x, y, z = -34, 36, -16$; $Z = 3.31$; $P < 0.05$ corrected). Activation in left DLPFC (BA 9/46) (Fig. 4b) was observed when the moderately abstract condition was compared to the other two conditions (peak $x, y, z = -46, 42, 24$; $Z = 3.24$; $P < 0.05$ corrected). Finally, activation in left RLPFC (BA 10/46) (Fig. 4c) was observed when the highly abstract mindset condition was compared to the other two conditions (peak $x, y, z = -38, 48, 0$; $Z = 3.81$; $P < 0.05$ corrected). No additional prefrontal areas of activation were observed even at a more lenient threshold ($P < 0.001$ uncorrected; see Table 1).

An examination of condition-specific contrast estimates for each of the three comparisons of interests (Fig. 5) confirmed that the observed increases in VLPFC, DLPFC, and RLPFC activation were specific to the corresponding comparison of interest and that there were no subthreshold activations present for the remaining two comparisons. Activations outside of PFC were observed only at a relatively lenient threshold ($P < 0.001$ uncorrected) and were restricted to the occipital cortex and its adjacent regions (Table 2).

Table 1 – Foci for activation maps shown on Figure 4.

Region	BA	Coordinates			No. of voxels	Peak Z-score	P-value
		x	y	z			
<i>a. Concrete</i>							
Left IFG	47/11	-34	36	-16	33	3.31	$< 0.05^a$
Left MOG	19/18	-50	-82	12	21	3.06	$< 0.001^b$
<i>b. Moderately abstract</i>							
Left MFG	9/46	-46	42	24	56	3.24	$< 0.05^a$
Left LingG	17	-6	-90	-8	19	3.48	$< 0.001^b$
<i>c. Highly abstract</i>							
Left MFG	10	-38	48	0	44	3.81	$< 0.05^a$
Left MOG	18	-12	-86	20	31	3.83	$< 0.001^b$
Left LingG	19	-16	-60	0	55	3.87	$< 0.001^b$
Right MOG	18	12	-90	16	33	4.40	$< 0.001^b$
Right LingG	18	4	-66	4	11	3.24	$< 0.001^b$

Abbreviations: BA, Brodmann area; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; MOG, middle occipital gyrus; LingG, lingual gyrus.

^aCorrected for multiple comparisons within the a priori defined region of interest.

^bUncorrected for multiple comparisons.

To quantify the distance between the centers of activation in the observed prefrontal regions, we performed a multivariate statistical test using Hotelling's T^2 statistic. The local maxima of activation from individual subjects' analyses were extracted ($P < 0.05$ corrected) and compared in the x , y , and z dimensions, treating them as three-dimensional clusters of observations. The distance between the peaks of activation in

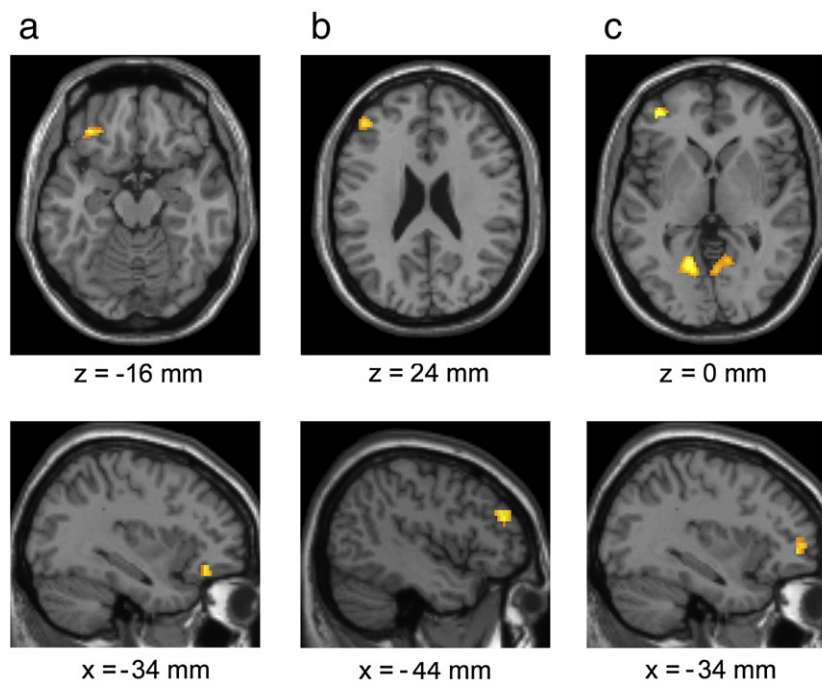


Fig. 4 – Topographical prefrontal recruitment at different levels of representational abstraction. Regions of activation during (a) concrete, (b) moderately abstract and (c) highly abstract anagram blocks are displayed in axial and sagittal orientations and superimposed on an averaged T1-weighted magnetic resonance image at a threshold of $P < 0.001$.

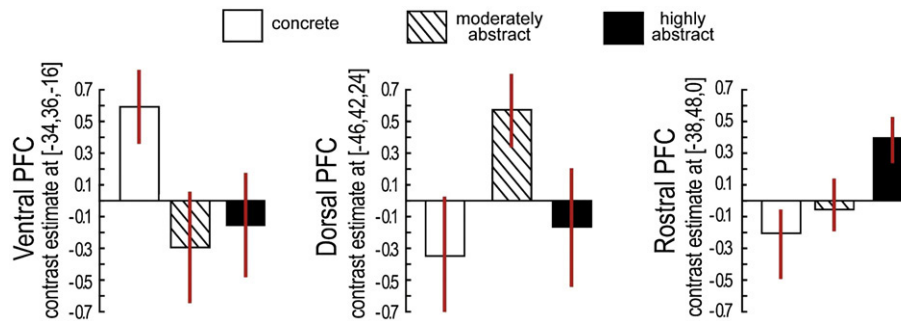


Fig. 5 – Condition-specific contrast estimates and 90% confidence intervals for the peak voxels of activation in rostral, dorsal and ventral PFC. Each contrast estimate was derived by comparing the corresponding anagram condition to the remaining two conditions (concrete anagrams were contrasted against the combined moderately abstract and highly abstract anagrams; highly abstract anagrams were contrasted against the combined highly concrete and moderately abstract anagrams, and so on).

the highly abstract and moderately abstract clusters was 26 mm (Hotelling's $T^2=34.78$, $F_{2,29}=16.91$, $P<0.001$); between the moderately abstract and concrete cluster, 42.2 mm ($T^2=79.08$, $F_{2,29}=38.22$, $P<0.001$); and between the highly abstract and concrete clusters, 20.4 mm ($T^2=13.76$, $F_{2,29}=6.65$, $P<0.005$). Thus, the observed prefrontal activations formed separate clusters in three-dimensional space.

To verify that the observed activations were due to the adoption of mindsets at different levels of abstraction, rather than the processing of solution words per se, an additional analysis was conducted including only trials in which subjects were unable to solve the anagrams (trials for which subjects did not arrive at a solution). The same pattern of prefrontal recruitment was observed for the three comparisons of interest, with increased relative recruitment of left RLPFC for highly abstract mindset (peak $x,y,z=-22, 56, 8$; $Z=2.58$; $P<0.005$), left DLPFC for moderately abstract mindset (peak $x,y,z=-46, 50, 20$; $Z=2.89$; $P<0.005$), and left VLPFC for concrete mindset (peak $x,y,z=-34, 28, -12$; $Z=2.76$; $P<0.005$). Similarly to the analysis including all trials, no additional prefrontal cortex activations were observed for any of the three comparisons of interest.

Finally, the observed pattern of prefrontal cortex recruitment was observed independently of individual differences in anagram solution ability. While average solution accuracy varied considerably across subjects, the accuracy for a given condition did not correlate with the extent to which subjects activated the hypothesized prefrontal region for this condition ($P>0.57$ for all three correlations), suggesting once again that it was the process of attempting to solve an anagram solution rather than the process of successfully arriving at the solution that best accounts for the present results.

3. Discussion

This experiment aimed to test the prediction that different prefrontal subregions show preferential recruitment during the implementation of mindsets at different levels of abstraction. The observed pattern of results was consistent with this prediction. Mindsets for concrete information were associated with increased relative recruitment of a posterior PFC region

(VLPFC). Mindsets for moderately abstract information were associated with increased relative recruitment of a more anterior, mid-PFC region (DLPFC). Finally, mindsets for highly abstract information were associated with increased relative recruitment of the most anterior lateral PFC region (RLPFC). Thus, information at increasing level of abstraction was generally associated with increasingly anterior PFC subregions.

The observed pattern of results was obtained in the absence of difference in behavioral difficulty across conditions, as indicated by comparable reaction times and accuracy, demonstrating that representations at varying levels of abstraction can drive prefrontal recruitment independently of task difficulty. Furthermore, the same pattern of prefrontal recruitment remained evident when analysis was limited to trials on which subjects were unable to reach a solution, suggesting that cognitive control processes related to adoption of a mindset were responsible for the observed results rather than the processing of solution words per se. Finally, individual differences in anagram solution ability were not related to the extent to which subjects activated each prefrontal subregion in its corresponding level of abstraction.

While a number of theories have proposed posterior-to-anterior mapping of cognitive control processes within the lateral PFC (Fuster, 1980; Christoff and Gabrieli, 2000; Koehn et al., 2003; Badre and D'Esposito, 2007), their experimental demonstration has been beset by the strong association between increases in task difficulty and the progressive recruitment of PFC subregions in an increasingly anterior direction. To our knowledge, the present results provide the first experimental demonstration that it is possible to observe recruitment of successive, discrete PFC subregions arranged in a general posterior-to-anterior fashion, in the absence of variations in task difficulty. In addition, our results are consistent with previous findings that DLPFC recruitment can occur independently of variations in task difficulty (Barch et al., 1997; Bor et al., 2003; Han et al., 2009), and serve to extend these findings by showing this is also possible to demonstrate for two other lateral PFC regions, VLPFC and RLPFC.

While a general posterior-to-anterior displacement of activation was observed with increasing order of abstraction, the specific prefrontal subregions that were identified were

not arranged in a strictly linear fashion but instead followed a curvilinear trend: The VLPFC region of activation was located lowest in terms of its z-coordinate location, the DLPFC region was highest, and the RLPFC region was in between the other two. The specific regions of activation that were identified are only subparts of VLPFC, DLPFC, and RLPFC, and it is possible that their specific arrangement may be different if different tasks or cognitive processes were to be examined. The anatomical location of these three prefrontal regions, however, also suggests a curvilinear arrangement in the three-dimensional coordinate system (e.g., Petrides, 2005) (also, see Fig. 1). In addition, other studies have identified different gradients of abstraction located more dorsally within the prefrontal cortex, spanning the distance between the premotor cortex and anterior PFC (Koechlin et al., 2003; Badre and D'Esposito, 2007). These findings suggest that rather than implementing a single, fixed, and strictly linear posterior-to-anterior gradient of abstraction, the PFC may be able to realize multiple possible gradients that could differ according to the specific prefrontal subregions involved in a given task. Finally, because of the complex cortical topography and gyration, what is linear in the 3-dimensional space is not necessarily linear in functional cortical space as clearly demonstrated by cortical unfolding techniques (Van Essen et al., 1998; Fischl et al., 1999). Only future studies that use such precise cortical unfolding techniques to examine prefrontal cortex functions will be able to elucidate the precise arrangement of abstraction gradients that PFC can implement.

The present results bear implications for understanding the functions of the most anterior lateral PFC region, the RLPFC, whose role in human cognition continues to pose challenges to our neuroscientific theories. RLPFC recruitment has been linked to conditions of high task complexity more consistently than any other PFC subregion (Christoff and Owen, 2006). It is activated during some of the most complex forms of human cognition, including inductive and deductive inferences during reasoning (e.g., Christoff et al., 2001; Monti et al., 2007), hypothesis testing and set shifting during problem solving (Berman et al., 1995; Goel and Vartanian, 2005), and subgoal processing during planning and coordination of multiple tasks (e.g., Koechlin et al., 1999; Braver and Bongiolatti, 2002; Ramnani and Owen, 2004). The link between RLPFC recruitment and task complexity is so consistent that its sensitivity to cognitive complexity has been proposed to represent one of the defining features of its functions (Christoff and Owen, 2006; Gilbert et al., 2006). Perhaps the biggest paradox of RLPFC functions, however, is presented by findings of its activation not only during highly complex tasks, but also during conditions of “rest” when tasks are altogether absent (Shulman et al., 1997; Christoff et al., 2004; Christoff et al., *in press*) and by mind wandering, especially when individuals are unaware of the fact that they are mind wandering (Christoff et al., 2009).

The present results could provide clues towards understanding the seemingly paradoxical recruitment of RLPFC during highly complex tasks and conditions of “rest”. Both situations may increase opportunities for processing highly abstract information: difficult tasks – by posing complex processing demands, and the absence of tasks – by allowing attention to be directed towards the internal world and away

from immediate perceptual information, a process considered to be characteristic of RLPFC function (Christoff and Gabrieli, 2000; Christoff et al., 2001; Christoff et al., 2003; Burgess et al., 2005; Burgess et al., 2007). In addition, the present findings are significant in demonstrating that a variation in task complexity by itself is not a necessary condition for RLPFC recruitment. Instead, they suggest that the systematic connection between task difficulty and RLPFC recruitment could be mediated by a third factor: increasing demands for the processing of highly abstract information. Finally, a role for RLPFC in implementing highly abstract mindsets is also consistent with recent findings demonstrating recruitment of this region when individuals engage in aesthetic appreciation of artwork (Cupchik et al., 2009), a process considered to involve an attentional shift away from perceptual features and towards highly abstract aspects of the perceived artwork and associated internal experiences (Cupchik, 1992; Cupchik and Winston, 1996).

Two kinds of processes are thought to be at work during anagram solution. On the one hand, an analytic search process may be used to carry out a deliberate search of the lexicon for orthographically regular sub-sequences of the given letters (Richardson and Johnson, 1980). On the other hand, more automatic search processes can lead to a sudden awareness of the solution, a phenomenon known as “insight” (Metcalfe and Wiebe, 1987; Sternberg and Davidson, 1995; Bowden et al., 2005). While analytic and insight search processes are distinguishable at the theoretical and neural levels (Metcalfe and Wiebe, 1987; Sternberg and Davidson, 1995; Bowden and Jung-Beeman, 2003; Jung-Beeman et al., 2004; Gilhooly et al., 2005; Kounios et al., 2006), they are not mutually exclusive and can occur in parallel (Kounios et al., 2008). The present study examined the effects of implementing a mindset at different levels of abstraction without distinguishing between these different types of search processes. It remains a subject for future research to examine whether the implementation of mindset would differ depending on whether more deliberate or more automatic search processes are primarily employed.

The notion of hierarchical organization has been a recurrent topic in theories of prefrontal function (for a recent review see Botvinick, 2008). Prefrontal hierarchy has often been described in processing terms, with more anterior regions assumed to work by re-representing the products of processes performed by more posterior regions (Christoff and Gabrieli, 2000; Fletcher and Henson, 2001; Badre and D'Esposito, 2007). Undoubtedly, presenting subjects with hierarchically structured tasks involving a sequence of mental operations, whereby each step relies upon the products of previous steps, is a reliable way to produce increasingly anterior recruitment. The present study, however, observed successive recruitment of prefrontal regions in the absence of such hierarchical differences across conditions; no additional processing steps were required by conditions that activated more anterior PFC subregions. These results suggest that being engaged in a complex, hierarchically structured task is not a necessary condition for the recruitment of anterior PFC subregions. Furthermore, recent work in computational modeling suggests that a fixed, strictly hierarchical arrangement of representations in the prefrontal cortex is not only

unnecessary for the implementation of hierarchical behavior, but could even pose potential limitations on behavioral flexibility (Botvinick, 2007). It seems likely, therefore, that rather than being a permanent characteristic of prefrontal function, a hierarchical processing arrangement is only one of the ways in which PFC can organize itself to meet current task demands.

The hereby observed functional organization according to level of abstraction in mindset suggests another principle according to which PFC can adaptively organize itself. An organization according to level of abstraction in representation is consistent with findings from human development that have linked the continually increasing abstract representational capacity through childhood and adolescence (Fischer and Rose, 1994, 1996; Fischer and Bidell, 2006) to the maturation of PFC in a progressively anterior direction (Diamond, 1991; Bunge and Zelazo, 2006; Crone et al., 2009). The importance of this maturation gradient for prefrontal organization has also been the subject of recent computational modeling work (Reynolds and O'Reilly, in press). Finally, studies of anatomical connectivity between prefrontal cortex and other posterior cortical regions (e.g., the temporal and parietal cortices) suggest a pattern of connectivity in which increasingly anterior PFC regions are preferentially connected to posterior cortical areas representing information at increasing higher orders of association (Pandya and Barnes, 1987). Thus, a relative preference for abstract representations in more anterior PFC regions may emerge through the combined probabilistic constraints posed by patterns of anatomical connectivity and brain maturation.

Rather than demonstrating an absolute specialization according to level of abstraction, we interpret the present results as indicative of a relative or statistical specialization (Duncan, 2001). Such relative specialization would be consistent with findings of substantial adaptability of function at the level of single neurons (Miller, 2000; Miller and Cohen, 2001). These findings lie at the basis of the adaptive coding model of prefrontal function (Duncan, 2001), according to which neurons throughout the lateral prefrontal cortex can flexibly adapt their properties and representational tuning to carry currently relevant information. A relative specialization for different levels of abstraction may add to this adaptability of function, allowing PFC neurons to organize flexibly so that relevant information can be represented at different levels of abstraction in separate prefrontal regions. Furthermore, the process of building abstract mental representations entails the selection of relevant and exclusion of irrelevant information from a group of objects or experiences (Mar and Oatley, 2008), which could explain why PFC appears to play a key role in both selective attention (Desimone and Duncan, 1995) and the processing of abstract information.

Finally, the ability to implement separate representations at different levels of abstraction may account for the central role of PFC in hierarchical updating—a crucial feature of higher cognition (Miller and Cohen, 2001; Rougier et al., 2005) that allows for the updating of concrete representations, such as particular moves or actions, while preserving more abstract representations, such as the overall strategy being pursued. It may also provide clues towards understanding the role of PFC in self-regulation and decision-making—processes that often rely on balancing concrete, immediate concerns with more

abstract, distant goals (Mischel et al., 1989; Trope et al., 2000). Lesion studies have suggested that human behavior is structured by a set of action constraints or requirements specified at multiple levels of abstraction (Duncan et al., 1996). Thus, a relative specialization of separate PFC subregions to represent information at different levels of abstraction, in combination with their ability to become adaptively tuned to currently relevant information, may ultimately help explain the unique flexibility and complexity of human behavior.

4. Experimental procedures

4.1. Subjects

Sixteen right-handed volunteers (eight female) from the University of British Columbia community took part in the experiment. Subjects were 18 to 24 years old ($M=20.3$, $SD=1.37$), had no psychiatric history, and were native English speakers. Data from three additional subjects were collected but excluded from analysis, one due to excessive motion (3.39 mm translation in the z-dimension) and the other two due to significant task-correlated motion ($P<0.001$) in head rotations. All subjects gave informed, written consent to participate in the experiment. The study was approved by the Clinical Research Ethics Board at the University of British Columbia.

4.2. Stimuli

Anagrams were generated by scrambling selected nouns from the MRC Psycholinguistics database (Wilson, 1988). A total of 288 nouns were selected, with abstractness ratings according to Paivio et al. (1968), ranging from 100 (highly abstract) to 700 (highly concrete). The nouns were divided into 3 groups: *highly abstract* (range 200–350, $M=304$, $SD=28.54$), *moderately abstract* ($M=466$, $SD=46.34$, range 375–525), and *concrete* ($M=585$, $SD=20.34$, range 550–700), with each group containing 96 nouns. Words were chosen to have unique solutions in order to minimize semantic ambiguity (Safren, 1962; Dominowski and Ekstrand, 1967; Greeno, 1978; Schuberth et al., 1979; Richardson and Johnson, 1980; Seidenstadt, 1982). The three conditions were matched for word length ($M=5.4$ letters long, $SD=1.04$, range 4–7), number of syllables ($M=1.5$, $SD=0.5$, range 1–2), and Kucera and Francis (1967) corpus word frequency ($M=54.1$, $SD=36.7$, range 5–150).

The amount of unscrambling necessary to solve anagrams in each condition was assessed by calculating the number of letter moves necessary to solve each anagram. (A letter move was defined as the removal and re-insertion of one letter within an anagram.) The range for each condition was 1 to 3 moves. The mean number of letter moves in the highly abstract, moderately abstract, and concrete conditions was 1.64 ($S.D.=0.55$), 1.54 ($S.D.=0.58$), and 1.77 ($S.D.=0.47$), respectively. There was no significant difference in the number of letter moves between the highly abstract and moderately abstract conditions ($T=1.23$, $df=190$, $P>0.05$, Cohen's $d=0.18$). Importantly, anagrams in the concrete condition did not require fewer letter moves to be solved than anagrams in the two abstract condition; if

anything, concrete anagrams required a fractionally higher number of moves compared to anagrams in the highly abstract ($T=1.76$, $df=190$, $P<0.1$, Cohen's $d=0.25$) and moderately abstract ($T=3.02$, $df=190$, $P<0.05$, Cohen's $d=0.43$) conditions. Thus, there was no significant increase in the number of moves necessary to solve anagrams from the most concrete to the most abstract conditions.

To facilitate the process of reaching a solution, either the first letter (for 4- and 5-letter anagrams) or the first two letters (for 6- and 7-letter anagrams) of each anagram were placed in the correct positions, as indicated by capitalization (e.g. "H r m a" and "L E r t e t"). This method of cuing subjects with the correct initial letter(s) has been previously demonstrated to facilitate the solution process (e.g., Murray and Mastronardi, 1975). Behavioral piloting was conducted prior to the fMRI study to match the anagrams from the three conditions as close as possible in terms of accuracy and response times.

4.3. Behavioral procedure

The experiment comprised two scanning sessions, during which subjects solved anagrams grouped in blocks according to their solutions' level of abstraction (Fig. 2). Each session included six highly abstract, six moderately abstract and six concrete blocks, presented in pseudorandom order across subjects. Each block was 34 s long, and began with a 2 s instruction period, during which a cue word appeared, indicating the level of abstraction of solutions in the subsequent block. The words "Abstract," "Medium," and "Concrete" were used as cues for the highly abstract, moderately abstract, and concrete conditions, respectively. Subjects were instructed to use that cue to help them in limiting the number of possible solutions they were considering. The cue remained on-screen for the duration of each block. After the instruction period, an anagram appeared in the center of the screen every 4 s, for a total of 8 anagrams per block. Subjects were given 4 s from the onset of each anagram to respond. Anagrams remained on the screen until the response, but no longer than 3.5 s, thus allowing for at least a 500 ms inter-stimulus interval.

Subjects were instructed to press a button as soon as they solved each anagram, and then to say the solution aloud. To allow spoken responses to be recorded, a clustered fMRI acquisition sequence (Edmister et al., 1999) was employed during which silent periods (1000 ms) alternated with fMRI acquisition periods (1000 ms). The button press was used to measure the response time, and the spoken solution to measure accuracy.

Before scanning, subjects were given a 5 min practice session. During scanning, stimuli were presented on a screen located above the subject's head, using a magnet-compatible back projection method. Subjects responded with their right hand, using their index finger to press a button on a hand-held button-box.

4.4. fMRI data acquisition

Imaging was performed using a 3.0 T Philips Intera MRI scanner (Best, Netherlands). An eight-element, six-channel

phased array head coil with parallel imaging capability (SENSE) (Pruessman et al., 1999) was positioned around the subject's head to obtain the MRI signal. Head movement was restricted using foam padding around the head. Functional volumes were acquired using a clustered volume acquisition sequence (Edmister et al., 1999) with a time of repetition (TR) of 2000 ms. The feasibility of combining clustered volume acquisition with parallel imaging (SENSE) has been demonstrated previously (Scheef et al., 2005). All slices within a volume were acquired within the first 1000 ms of the TR, leaving a quiet period of 1000 ms in the second half of the TR, during which subjects could respond by saying the answer aloud. The functional volumes contained BOLD contrast intensity values and were acquired using a T2*-weighted single shot echo-planar imaging (EPI) gradient echo sequence sensitive to BOLD contrast [echo time (TE)=30 ms; flip angle (FA)=90°; field of view (FOV)=24×24 cm²; matrix size 80×80, reconstructed to 128×128, SENSE factor=2.0].

The volumes covered the whole brain and consisted of 19 slices (each 6 mm thick, separated by a 1 mm inter-slice gap) acquired parallel to the anterior commissure/posterior commissure (AC/PC) line. A total of 712 functional volumes were acquired for each subject over 24 min (2 sessions, 12 min each). Four discarded volumes (a total of 8 s) were acquired at the beginning of each session to allow for longitudinal relaxation steady state (T1) and eddy current stabilization.

Prior to functional imaging, an inversion recovery prepared T1-weighted fast spin-echo anatomic volume was obtained for each subject (TR=2000 ms; TE=10 ms; spin-echo turbo factor=8, FA=90°; FOV=24×24 cm²; 256×256 voxels, inversion delay IR=800 ms). It contained 19 slices (6 thick, separated by 1 mm skip) acquired in the same slice locations used for functional images and allowed for subsequent anatomical localization of functional activation.

4.5. fMRI data analysis

Data were preprocessed and analyzed using SPM5 (Statistical Parametric Mapping; Wellcome department of Cognitive Neurology, London, UK). To account for the different sampling times of the different slices, voxel time series were interpolated using sinc interpolation and resampled using the middle (tenth) slice as a reference point. All functional volumes were realigned to the first one in the time series to correct for between-scan motion. The structural T1-weighted volume was segmented to extract a gray matter image for each subject, which was spatially normalized (Ashburner and Friston, 1999) to a gray matter image of the MNI template. The derived spatial transformations for each subject were applied to the realigned functional volumes, in order to bring them into standardized MNI space. After normalization, all volumes were resampled in 2×2×4 mm voxels using sinc interpolation in space. Finally, all T2*-weighted volumes were smoothed with an 8-mm full width at half-maximum (FWHM) isotropic Gaussian kernel to compensate for residual between-subject variability after spatial normalization and permit application of Gaussian random field theory to provide for corrected statistical inference (Friston et al., 1994).

Statistical analysis was performed at each voxel to assess the magnitude of differences between conditions in the three comparisons of interest. An anatomically defined gray matter mask was created and explicitly specified to ensure that statistical analysis was performed in all brain regions, including those where signal may be low due to susceptibility artifacts. To remove low-frequency drift in the BOLD signal, data were high-pass filtered using an upper cut-off period of 128 s. No global scaling was performed.

Condition effects at each voxel were estimated according to the general linear model (Friston et al., 1995). The model included: i) the observed time series of intensity values, representing the dependent variable; ii) covariates modeling session-specific effects, later treated as confounds; and iii) regressor functions constructed by convolving condition-specific box-car functions with a synthetic hemodynamic response function (HRF). Four such regressor functions were included: three blocked design regressors modeling each level of abstraction and one event-related regressor modeling the onset of instructions across all conditions. Regressors corresponded to the 32 s post-instruction periods for each block comprising the condition. Regionally specific effects were estimated using linear contrasts to compare the parameter estimates for regressors modeling each condition of interest (highly abstract, moderately abstract, and concrete), compared to the other two conditions. The three comparisons of interest were: i) highly abstract versus moderately abstract and concrete; ii) moderately abstract versus highly abstract and concrete; and iii) concrete versus highly abstract and moderately abstract. These contrasts were defined by assigning a weight of 1 to the condition of interest and weights of -0.5 to the other two conditions.

Group analysis was performed using a random effects model, by entering the estimated individual contrast images into a voxel-specific regression across subjects. The resulting *t*-maps were subsequently transformed to the unit normal *Z*-distribution to create a statistical parametric map for each contrast. In view of the hypothesis of a prefrontal topography according to level of abstraction in representation, we created three regions of interest using anatomical labels from the Talairach Daemon database, (http://ric.uthscsa.edu/RIC_WWW.data/Components/talairach/talairachdaemon.html), corresponding to the anterior, middle, and posterior third of the lateral prefrontal cortex. Within these a priori regions of interest, the threshold for significance was set at $P < 0.05$ corrected for multiple comparisons. Threshold for significance elsewhere in the brain was set at voxel level $P < 0.05$ corrected for multiple comparisons across the entire gray matter volume. In addition, areas of activation throughout the brain were examined at a more lenient threshold ($P < 0.001$ uncorrected) to assess whether subthreshold activations were present. The foci of maximum activation were localized on an anatomical image created by averaging the normalized individual *T1*-weighted images. The location of these maxima in terms of Brodmann areas (Brodmann, 1908) was determined using the nomenclature given by Talairach and Tournoux (1988).

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