Dissociable Contributions of Left and Right Dorsolateral Prefrontal Cortex in Planning

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It is well established that the mid-dorsolateral prefrontal cortex (dlPFC) plays a critical role in planning. Neuroimaging studies have yielded predominantly bilateral dlPFC activations, but the existence and nature of functionally specific contributions of left and right dlPFC have remained elusive. In recent experiments, 2 independent parameters have been identified which substantially determine planning: 1) the degree of interdependence between consecutive steps (search depth) and 2) the degree to which the configuration of the goal state renders the order of single steps either clearly evident or ambiguous (goal hierarchy). Thus, search depth affects the actual mental generation and evaluation of action sequences, whereas goal hierarchy reflects the extraction of goal information from an encountered problem. Here, both parameters were independently manipulated in an event-related functional magnetic resonance imaging study using the Tower of London task. Results revealed a double dissociation as indicated by a significant crossover interaction of hemisphere and task parameter: in left dlPFC, activations were stronger for higher demands on goal hierarchy than on search depth, whereas the reversed result emerged in right dlPFC. In conclusion, often observed bilateral patterns of dlPFC activation in complex tasks may reflect the concomitant operation of specific cognitive processes that show opposing lateralizations.

Keywords: dissociation, executive functions, fMRI, lateralization, prefrontal cortex

Introduction

Planning is crucial for efficient performance in a wide range of situations. As expected from its proposed role in the organization of overt and covert action, the mid-dorsolateral prefrontal cortex (dlPFC) was found to play a critical role in the neural network subserving the planning of action sequences (Owen 2005; Tanji et al. 2007), that is, the purely mental conception and evaluation of behavioral sequences and associated outcomes before their execution (Goel 2002; Unterrainer and Owen 2006). Yet, the existence and nature of differential contributions of left versus right dlPFC have remained controversial (Cazalis et al. 2003). Evidence from neuroimaging experiments, using the Tower of London (ToL) planning test (Shallice 1982), have mostly reported bilateral dlPFC activations (Tables 1 and 2). Consequently, the question arises whether this predominance of bilateral dlPFC activations reflects the recruitment of homologous resources across hemispheres due to high demands imposed by task complexity. As an alternative, the pattern may also be caused by the concomitant activity of multiple presumably separable pro-

cesses that differentially engage either left or right dlPFC (Grafman et al. 2005).

Here, we sought to identify and characterize these potentially specific contributions of left versus right dlPFC in the context of planning. Building on consistent evidence from a series of recent behavioral experiments (Ward and Allport 1997; Kaller et al. 2004; Unterrainer, Rahm, et al. 2005; Newman and Pittman 2007; Berg et al. 2010), we employed an event-related functional magnetic resonance imaging (fMRI) paradigm that allowed for a separation of 2 main determinants of planning demands: 1) the degree of interdependence between consecutive steps of the planned sequence (search depth) and 2) the degree to which the exact order of this sequence may be deduced from the goal state (goal hierarchy)(for further details, see also Fig. 1 and Materials and Methods).

In terms of cognitive processing, search depth and goal hierarchy have been previously shown to have differential roles in planning (Kaller et al. 2004, 2008; McKinlay et al. 2008). The use of goal hierarchy reflects the extraction of information from an encountered problem by structurally analyzing the goal state. To give an example, imagine you just arrived home when the phone rings and an old friend announces that he will drop in at short notice within the next hour. You abruptly realize that you have to manage several goals before your friend arrives: you should offer at least some pasta for dinner. However, your kitchen is in a mess and you have hence to do a huge pile of dirty dishes. Since kitchen utensils such as pots, knife, spoon, and board are minimum prerequisites for preparing pasta with a basic tomato sauce, you will have to start with cleaning up. So, the order in which to work on your goals is not arbitrary but is completely identifiable from your overall goal. Likewise, in the ToL task, a goal state consisting of 3 balls stacked on a single rod allows to unambiguously deduce the sequence in which the balls have to be placed into their goal positions, that is, the bottommost ball has to be put there first, followed by the second and at last the topmost ball. When balls are distributed across pegs instead, this results in a partially ambiguous goal hierarchy that requires comparing and matching the identities and locations of balls across both the start state and the goal state (cf. Fig. 1). Thus, goal hierarchy reflects the degree to which a sequence for attaining several goals is identifiable from the goal state.

In contrast, search depth refers to the actual mental generation and evaluation of sequences as it requires the integration of individual moves while taking into account their interdependencies. To stay with our example, let us say, you have 2 alternatives, either washing dishes and kitchenware by hand or using the dishwasher. Both will equivalently serve the goal of having a clean kitchen. However, as a washing cycle in

Table 1

Laterality of dlPFC activity for comparing planning versus baseline conditions

References	Method	dlPFC activity
Morris et al. (1993)	SPECT	Left
Owen et al. (1996)*[1]	PET	Left
Owen et al. (1998)*[1]	PET	Left
Rowe et al. (2001)	PET	Left
Beauchamp et al. (2003)*[2]	PET	Left
Wagner et al. (2006)#[1]	fMRI	Left
Baker et al. (1996)*[3]	PET	Bilateral
Elliott et al. (1997)*[3]	PET	Bilateral
Lazeron et al. (2000)	fMRI	Bilateral
Cazalis et al. (2003)*[4]	fMRI	Bilateral
Newman et al. (2003)	fMRI	Bilateral
Schall et al. (2003)#[2]	fMRI	Bilateral
Lazeron et al. (2004)	fMRI	Bilateral
Van den Heuvel et al. (2005)	fMRI	Bilateral
Boghi, Rampado, et al. (2006)	fMRI	Bilateral
Boghi, Rasetti, et al. (2006)	fMRI	Bilateral
Just et al. (2007)	fMRI	Bilateral
Beauchamp et al. (2008)*[2]	fMRI	Bilateral
Den Braber et al. (2008)	fMRI	Bilateral
Fitzgerald et al. (2008)	fMRI	Bilateral
De Ruiter et al. (2009)	fMRI	Bilateral
Dagher et al. (1999)	PET	Right
Van den Heuvel et al. (2003)	fMRI	Right
Wagner et al. (2006)#[1]	fMRI	Right
Andreasen et al. (1992)	SPECT	No effect
Rezai et al. (1993)	SPECT	No effect
Dagher et al. (2001)	PET	Not reported
Cools et al. (2002)	PET	Not reported
Schall et al. (2003)#[2]	PET	Not reported
Unterrainer et al. (2004)*[5]	fMRI	Not reported
Unterrainer, Ruff, et al. (2005)*[5]	fMRI	Not reported
Rasser et al. (2005)	fMRI	Not reported
Cazalis et al. (2006)*[4]	fMRI	Not reported
Williams-Gray et al. (2007)	fMRI	Only patients

Note: Summary of all 32 neuroimaging studies on planning in the ToL task published until the end of 2008 that either could be found by a widespread Medline search (key word: "Tower of London") or were otherwise known to the authors. Only data of normal controls was considered. Numbered asterisks (*) indicate identical or overlapping samples across studies, whereas a hash (#) denotes different imaging methods and/or baseline conditions within studies.

Table 2

Laterality of dlPFC activity with respect to planning difficulty

References	Method	dlPFC activity
Schall et al. (2003)	PET	Left
	fMRI	Left
Elliott et al. (1997)*[1]	PET	Bilateral
Dagher et al. (1999)	PET	Bilateral
Dagher et al. (2001)	PET	Bilateral
Newman et al. (2003)	fMRI	Bilateral
Van den Heuvel et al. (2003)	fMRI	Bilateral
Unterrainer et al. (2004)	fMRI	Bilateral
Van den Heuvel et al. (2005)	fMRI	Bilateral
Wagner et al. (2006)	fMRI	Bilateral
Just et al. (2007)	fMRI	Bilateral
Den Braber et al. (2008)	fMRI	Bilateral
De Ruiter et al. (2009)	fMRI	Bilateral
Baker et al. (1996)*[1]	PET	Right
Lazeron et al. (2004)	fMRI	Right
Rasser et al. (2005)	fMRI	Right
Owen et al. (1996)*[2]	PET	No Effect
Owen et al. (1998)*[2]	PET	No Effect
Lazeron et al. (2000)	fMRI	No Effect

Note: This constricted overview includes only those neuroimaging studies on the ToL that have specifically reported comparisons related to task difficulty by either contrasting problems with higher versus problems with lower minimum numbers of moves or by parametrically testing across different levels of minimum moves. Only data of normal controls was considered. Numbered asterisks (*) indicate identical or overlapping samples across studies.

the dishwasher takes more than half an hour, this might get you in conflict with achieving your second goal in time since you cannot prepare and boil down a tomato sauce for the pasta while your pot, kitchen knife, spoon, and cutting board are in the machine. That is, you have to take into account the interdependencies between the different alternative steps to achieve your goals—and consequently, you have to wash all much-needed kitchen utensils by hand, whereas, for sake of time, you may put all remaining equipment in the dishwasher. With respect to the associated manipulation of search depth in the ToL task, the situation is quite similar: for problems with an intermediate move depicted in Figure 1, neither the white nor the gray ball can be directly placed into their goal positions, and there are 2 alternatives for initially moving the white ball in order to release the gray ball. However, only one choice for depositing the white ball leads to an optimal solution since the other will block the subsequent goal move of the gray ball (cf. Kaller et al. 2008). This interdependency thus clearly requires mentally looking ahead, whereas problems without an intermediate move can be solved in a straightforward manner, placing each ball in its goal position directly (Fig. 1).

Concerning the lateralization of prefrontal functions, Grafman et al. (2005) recently discussed left dlPFC functions in terms of structurally analyzing propositional information that make up a plan, whereas the right dlPFC was assumed to deal with the temporal and dynamic aspects of planning by mediating the integration of information into a sequence. One might hence suppose that goal hierarchy and search depth yield dissociable activations of left and right dlPFC, respectively.

In consequence, by applying a 2-factorial manipulation of search depth and goal hierarchy in the present study, we aimed to isolate their potentially differential impact on dlPFC lateralization. In line with this assumption, we found indeed a double dissociation between these task parameters and the observed lateralization of dlPFC activation.

Materials and Methods

Subjects

Thirty healthy volunteers aged between 19 and 39 years (mean: 26.3 years, standard deviation [SD]: 4.3; 12 men) participated in the present study. All were right-handed as assessed by the Salmaso and Longoni (1985) handedness inventory and had normal or corrected-to-normal vision. None of them was under medical treatment or reported a history of psychiatric or neurologic disorders. Written informed consent was obtained from all the subjects prior to the experiment. The study protocol was approved by local ethics authorities. Subjects received compensation of €25 for participation. The total size of the analyzed sample was 24 subjects since 6 subjects were excluded due to extreme deviations from group means in performance measures ($n = 2$) or latencies ($n = 4$; see below and Supplementary Fig. 3).

Experimental Task and Design

The ToL is a so-called disc-transfer paradigm that was originally developed to measure planning impairments in patients with frontal lesions (Shallice 1982). In the ToL, planning is required for an efficient transformation of a given start state into a desired goal state, that is, for an optimal solution within the minimum number of moves. The task's general scenario is knowledge lean and well defined with explicit specification of the start state, the goal state, the transformation operators, and their restrictions (Ward and Morris 2005). The classic version of the ToL consists of 3 differently colored balls placed on 3 vertical rods of different heights that may hold at maximum 1, 2, or 3 balls, respectively. In the present fMRI experiment, subjects were, however, administered a computerized 3-ball version of the Ward and Allport tower task (WATT3; Fig. 1), a variant of the ToL that consists of 3 equally sized rods (Ward and Allport 1997). The absence of any size
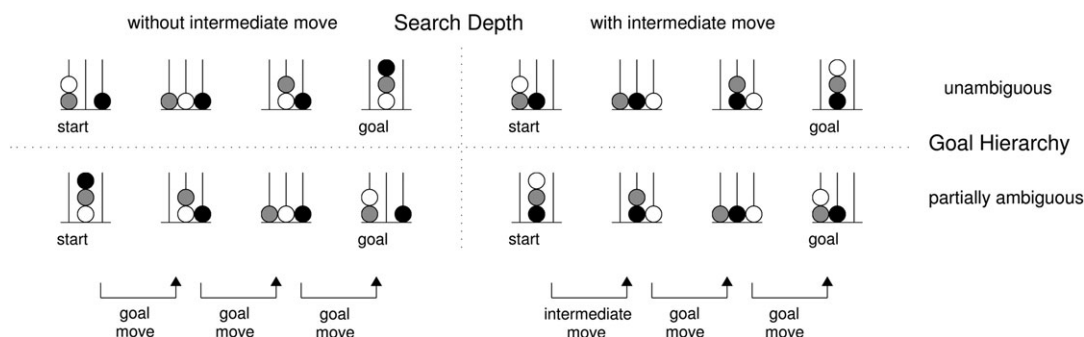
Figure 1. Experimental paradigm and design. In a set of 3-move problems, the task parameters search depth and goal hierarchy were experimentally manipulated within a 2 × 2 factorial design. Search depth involves the need to mentally accomplish intermediate moves and associated interdependencies. That is, even in relatively simple problems, it may be necessary not to put a ball into its goal position but somewhere else first in order to free the way for another ball to be placed into its respective final position (see the white ball in problems with an intermediate move). Goal hierarchy concerns the obviousness of priorities for individual goal moves that can be deduced from the structure of the goal state. That is, goal hierarchy relates to the possible configurations of the goal state that differentially predispose the consecutive order of the final goal moves. For instance, if all 3 balls are stacked on a single rod, the ball at the bottom definitely has to be in its goal position before the ball that is second from the bottom, and so on. See Materials and Methods for further details.

differences between rods makes the WATT3 more suitable for repeated presentations of structurally unique problems without subjects becoming aware of it. For this purpose, a basis set of problems (see Supplementary Fig. 1) was applied in various isoforms by pseudo-randomly permutating ball colors and rod arrangements thus giving structurally identical problems different looks (Berg and Byrd 2002; Unterrainer, Rahm, et al. 2005). Supplementary analyses further confirmed for the present data that intended experimental manipulations of goal hierarchy and search depth were not affected by block-wise repetitions of structurally unique problems (see Supplementary Fig. 2). Start state and goal state were presented in the lower and upper half of the screen, respectively. In order to match the goal configuration, subjects had to transform the start state by using a 3-button fMRI-compatible response box. More specifically, balls could be moved by a sequence of 2 button presses: A ball was initially "picked up" with a press on the response button that corresponded one-to-one with the location of the rod on which the ball was actually placed (i.e., "left" if the ball was placed on the left rod, "middle" for the middle rod, and "right" for the right rod). Accordingly, to place the ball on a certain rod, again the appropriate button had to be pressed. Thus, 1) only one ball could be moved at a time and 2) only the topmost ball on either rod could be moved.

As illustrated in Figure 1, the experiment was designed as a factorial manipulation of 2 task parameters, that is, search depth (with/without an intermediate move) and goal hierarchy (unambiguous/partially ambiguous). Search depth involves different demands on mentally constructing a sequence of interdependent steps depending on whether problems do or do not require an intermediate move. Intermediate moves are essential for an optimal solution but do not place a ball into its final goal position (Spitz et al. 1982; Kaller et al. 2004). In problems requiring an intermediate move, optimal solution can reliably be achieved only by taking into account the interdependence between the individual steps. In contrast, problems without an intermediate move may also be accomplished by pure forward processing based on simple perceptual matching-to-sample strategies (Owen 2005; Kaller et al. 2008), that is, placing each ball in its goal position in the straightforward ordering imposed by the goal state. In its original conception by Klahr and Robinson (1981), goal hierarchy concerns the obviousness of goal priority as evident from the structure of the goal state (see also Ward and Allport 1997; Kaller et al. 2004). Problems with "tower" goal states, in which all 3 balls are stacked on a single rod, provide an unambiguous goal hierarchy as the ball at the bottom definitely has to be in its goal position before the ball that is second from the bottom, and so on. Hence, the complete sequence in which the balls have to be placed in their goal positions is obvious from the goal state. In contrast, when the balls are distributed on 2 rods, as is the case for partially ambiguous goal states, information on the ordering of the final goal moves is only partially provided. To keep working memory demands at minimum, all applied

problems required only 3 moves for optimal solution. All selected problems had only one optimal path to solution (Unterrainer, Rahm, et al. 2005).

The fMRI experiment comprised a total of 96 experimental trials. That is, for each combination of the 2 × 2 factorial design (Fig. 1), 2 structurally unique problems were selected from the WATT3 problem space (see Supplementary Fig. 1) and each presented in 12 pseudorandomly selected isoforms. The presentation order of the problems was pseudorandom and carefully balanced so that regressors for fMRI modeling were orthogonal. More specifically, trial sequences were balanced so that each condition of the 2 × 2 design was equally frequently preceded and succeeded by itself and the remaining 3 other combinations. Task completion was self-paced with intertrial intervals varied pseudorandomly between 4.5 and 10.5 s. Presentation onset of problems was aligned to the MRI acquisition thereby using a jitter of 750 ms in 50% of trials. Individual problem sets were used. Besides emphasizing that solutions for moving the balls should always be planned in advance, subjects were asked also to complete the task as quickly and accurately as possible. Therefore, subjects were reminded of the instructions every 16 problems by written display on the screen ("Plan ahead first!"; "Work carefully but swiftly!"). Handling of the 3-button response box and movement execution was practiced a few days prior to the fMRI experiment with a set of 48 simple 1- and 2-ball problems. Subjects practiced again in a set of 8 three-move problems in the MR scanner immediately before the imaging experiment.

The following planning measures were recorded: solution accuracy, initial thinking, and movement execution times. Solution accuracy indicated whether a problem was solved in the minimum number of moves. Initial thinking time reflected the planning phase, that is, the interval from the presentation onset of a problem until the first selection of a ball, whereas movement execution time was defined as the time between the first uptake of a ball and the accomplishment of the last move, that is, the final solution of the problem.

Imaging Procedures

fMRI was performed on a 3.0 T whole-body MR scanner (Siemens TIM Trio) using a 8-channel head coil. Functional images were collected using 28 oblique axial slices fully covering the frontal and parietal lobes down to the superior part of the temporal lobe (slice thickness, 2.5 mm; gap, 0.5 mm; matrix size, 64 × 64; in-plane resolution, 3 × 3 mm; field of view [FOV], 192 mm) with a T_2^*-weighted echo-planar imaging sequence (repetition time [TR], 1500 ms; echo time [TE], 30 ms; flip angle [FA], 70°). The experiment comprised one single session which lasted between 18.5 and 23.7 min due to the self-paced design (mean, 21.3 min; SD, 1.3 min). On average, 850 functional images were acquired per subject (SD, 53; minimum, 741; maximum, 948). Image reconstruction was based on generalized autocalibrating partially

parallel acquisitions (GRAPPA; acceleration factor, 2). In-house algorithms were applied for online correction of motion and distortion artifacts (Zaitsev et al. 2004) so that functional images were unwarped and spatially aligned already before preprocessing in SPM5 (see below). High-resolution 3D T_1-weighted images were obtained with magnetization-prepared rapid gradient echo images (MPRAGE; TR, 2200 ms; TE, 2.15 ms; FA, 12°; 160 sagittal slices; matrix size, 256 × 256; FOV, 256 mm; 1.0 mm^3 cubic voxels).

Subjects lay supine on the scanner bed and responded with their right hand using a 3-button response box as described above. Stimuli were projected onto a screen mounted on the rear of the scanner bore and were viewed via a mirror system. To prevent excessive head motion, neck and side pillows were used to fixate subjects' heads inside the coil.

Behavioral Data Analyses

Prior to the behavioral and imaging analyses, subjects' individual means for accuracy, initial thinking, and movement execution times were examined for extreme deviations from group means. The reason behind this was to assure a high sample homogeneity as a basic prerequisite for appropriate statistical modeling of fMRI data. In a recursive procedure, 2 and 4 subjects were excluded that were more than 2.5 SDs (Hair et al. 2006) below/above group means of accuracy and initial thinking time, respectively (for further information, see Supplementary Fig. 3). Consequently, the total size of the analyzed sample was 24 of the initial 30 subjects.

Imaging Data Analyses

All preprocessing of imaging data and subsequent statistical analyses were performed using SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5). For each subject, functional images were slice-time corrected and coregistered to the anatomical scan. Subjects' anatomical scans were then used for calculation of transformation parameters for normalizing the functional images into the Montreal Neurological Institute space. Normalization estimates were based on segmentation routines as implemented in the voxel-based morphometry (VBM) toolbox for SPM5. Normalized functional images were resampled to 2 mm^3 and then spatially smoothed with an isotropic Gaussian kernel with a full width at half maximum of 8 mm.

For estimation of the hemodynamic response, subject-wise first-level analyses of imaging data were based on a finite impulse response (FIR) model with 8 basis functions with bin lengths of 2 s, thus covering a time window of 16 s. Previous behavioral experiments in combination with eye movement recordings had provided strong evidence that problem solving occurs in stages (Hodgson et al. 2000) with formation of an internal representation of the presented problem and planning operations, the latter being focused to the time window just before the start of movement execution (Kaller et al. 2009). Accordingly, to optimize modeling of planning-related activation, onset vectors were temporally aligned to the first uptake of a ball in each trial. Furthermore, all onset vectors were shifted to the time range from –5 s before to 11 s after the end of the initial planning phase. Hereby, FIR modeling was expected to capture planning-related brain activation in particular, given the observed mean initial thinking times of approximately 3 to 4 s that conformed well to findings from previous experiments (cf. Kaller et al. 2004, 2009). Besides regressors for each experimental condition, the instruction intervals as well as 6 additional head movement parameters estimated during online motion correction were modeled as effects of no interest. Before estimation, a standard 128 s temporal high-pass filter was applied to remove low-frequency noise from the data. Temporal autocorrelation was removed using a first-order autoregressive model. First-level estimates of the individual effects per condition and FIR time bin were then entered into a second-level random effects analysis of variance (ANOVA). F-tests were performed on individual bins entered as separate rows of the contrast matrices, thus testing for the presence of effects in any included bin. To account for multiple comparisons, statistical significance of activations was assessed at a corrected threshold of $P < 0.05$ based on the family-wise error (FWE) rate. Additionally, results are reported at a threshold of $P < 0.0001$ uncorrected for multiple comparisons and a minimum

cluster extent of $k > 20$ voxels. This liberal threshold was selected to assure detection of activation in both hemispheres in order to assess the lateralization of dlPFC activation, thereby avoiding potentially higher rates of false negative results due to limited statistical power (Duncan and Owen 2000b). Testing for the presence of interhemispheric differences in functional processing followed the rationale defined by Henson (2005, 2006). The formal requirements claiming a double dissociation were 1) a significant crossover interaction effect between regions and conditions in a repeated-measurements ANOVA, 2) the presence of at least one significant main effect of either condition versus baseline in each hemisphere, and 3) the absence of sign differences of activation across hemispheres. While the interaction pattern was the essential requirement, the presence of significant main effects in the absence of sign differences served to validate that interhemispheric differences were driven by 2 processes and not just by a single one that acted with opposing signs on both sides due to reciprocal connections (Henson 2005, 2006). For these interregional comparisons, supplementary volume-of-interest (VOI) analyses were performed using custom procedures written in Matlab (The Mathworks, Inc.). After conversion into percent signal change, condition-wise parameter estimates from the first-level models were individually extracted by taking the first eigenvariate across all time bins (i.e., basis functions) within a 15 mm radius spherical VOI at the Euclidian center of the left and right dlPFC group-level activation peaks for both goal hierarchy and search depth. Thereby, the risk of a double-dipping artifact was effectively avoided since subsequent VOI analyses were independent of the criteria for VOI selection (cf. Kriegeskorte et al. 2009).

Assignment of functional imaging results to anatomical structures was based on the SPM5 anatomy toolbox (Eickhoff et al. 2005).

Results

Accuracy

As expected, performance was very accurate and close to ceiling. Mean accuracy ranged from 94.4% to 98.7% across the factorial manipulations of task parameters. Due to this lack of variance, accuracy was not subject to further analyses.

Latencies

Repeated measurements analysis of variance (RM-ANOVA) of initial thinking times revealed significant main effects of both search depth ($F_{1,23} = 58.56$, $P < 0.001$) and goal hierarchy ($F_{1,23} = 16.85$, $P < 0.001$) but no interaction ($F_{1,23} = 0.98$, $P = 0.332$). Data are displayed in Figure 2A. RM-ANOVA of movement execution times revealed no effect for search depth ($F_{1,23} < 0.01$, $P = 0.986$) but a significant main effect for goal hierarchy ($F_{1,23} = 50.29$, $P < 0.001$) as well as a significant interaction ($F_{1,23} = 12.83$, $P = 0.002$). Data are displayed in Figure 2B.

Task-Dependent dlPFC Activation

Main effects of search depth and goal hierarchy revealed largely bilateral and overlapping activations in an extensive frontoparietal network (Fig. 3; see also Supplementary Tables 1 and 2). The interaction between both task parameters yielded only 2 small activation foci in the posterior bank of the right inferior frontal sulcus and in the right inferior parietal lobule (Supplementary Table 3).

For either hemisphere, post hoc inspection of parameter estimates revealed that for goal hierarchy, problems with a partially ambiguous goal state entailed stronger dlPFC activation than problems with an unambiguous goal state, whereas for search depth, problems requiring an intermediate move resulted in stronger dlPFC activation than problems without an intermediate move. While dlPFC showed significant activation in both hemispheres with respect to task manipulation, activation

patterns suggested an interaction between side and the 2 factors (Fig. 3; Table 3). However, since statistical testing of a double dissociation necessarily requires a direct comparison of regions within a single statistical model (Duncan and Owen 2000b; Henson 2005), we conducted additional VOI analyses.

A spherical VOI (radius 15 mm) was specified for each the left (−45 33 31) and the right dlPFC (40 38 34) at the Euclidian center of the most significant mid-dorsolateral activation peaks of the main effects of both goal hierarchy and search depth (see Table 3). Time courses for mean hemodynamic responses in left and right dlPFC VOIs following the different cognitive demands imposed by experimental manipulations of goal hierarchy and search depth are displayed in Figure 4.
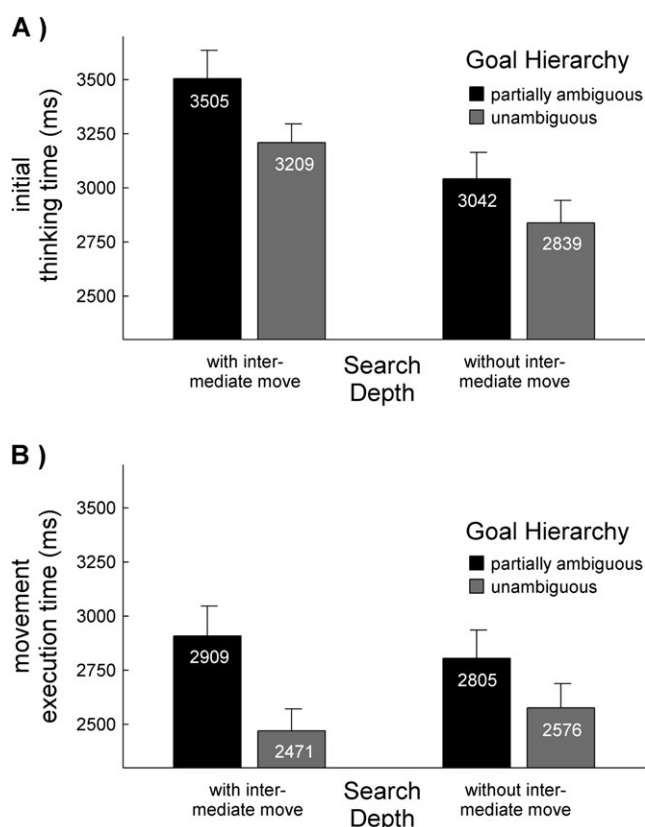
Figure 2. Latency analyses. Mean initial thinking times (*A*) and movement execution times (*B*) are plotted with respect to search depth and goal hierarchy that were experimentally manipulated in a 2 × 2 factorial design. Numbers within bars provide means, and error bars indicate standard error of means.

The average activation difference (for the interval from 0 to 8 s that captured the bulk of the hemodynamic response) was computed for each task parameter and individual VOI and entered as dependent variable in an RM-ANOVA on side (left/right) and task parameter (goal hierarchy/search depth). In line with the assumption of a functional dissociation of left and right dlPFC (Fig. 5*A*), results revealed a significant crossover interaction between side and task parameter ($F_{1,23} = 4.60$, $P = 0.043$) along with nonsignificant main effects for side ($F_{1,23} = 0.04$, $P = 0.845$) and task parameter ($F_{1,23} < 0.01$, $P = 0.950$).

The additional VOI analysis thus demonstrated that left and right dlPFC were differentially activated by the cognitive demands imposed by search depth and goal hierarchy. Yet, a crossed interaction, on its own, does not logically exclude the possibility that activation differences are driven by a single instead of 2 or more separate processes (cf. Dunn and Kirsner 1988), hence reflecting possibly a quantitative rather than a qualitative difference (Henson 2005). That is, anticorrelated networks, such as the "default mode" and "task demand" networks, are likely to demonstrate a significant task demand by region interaction that is still caused by a single process that influences the hemodynamic response of these regions with a different sign. This kind of interaction that rests on reciprocal connections can be ruled out (cf. Henson 2006), given that both left and right dlPFC showed increased activations at an FWE-corrected threshold for at least one of the task parameter manipulations (left dlPFC: goal hierarchy; right dlPFC: search depth), and that both regions showed positive responses versus baseline (Figs 4 and 5*A*).

Thus, the preceding VOI analysis statistically confirmed the presence of an actual double dissociation, that is, a qualitative difference of cognitive processing between left and right dlPFC. However, a caveat remains: A greater spatial extent of activation for goal hierarchy and search depth in left and right dlPFC, respectively, may have—at least to some extent—biased VOI analysis to favor one function over the other. We therefore checked that the results were also found using smaller VOI diameters and separately defined VOIs for each main effect and that in consequence the double dissociation was independent of a specific way of VOI definition.

Regional Specificity within Prefrontal Cortex
In order to test for the regional specificity of the double dissociation revealed for the dlPFC, we specified another 2 separate spherical VOIs (radius 15 mm) at the strongest bifrontal activation sites for the main effects of both goal hierarchy and search depth (cf. Fig. 3) that were located in the superior frontal gyrus and corresponded anatomically to the

Figure 3. Task-dependent activation of left and right dlPFC. Activation patterns related to the main effects of goal hierarchy (left side) and search depth (right side) at a voxel-wise threshold of $P < 0.0001$ (uncorrected; $F > 4.05$; cluster size $k > 20$ voxels). In the coronar views, planes were selected that contained the dlPFC activation maxima for goal hierarchy ($y = 32$) and search depth ($y = 36$). Activations are displayed on an average brain template created from the segmented and normalized brains of all included subjects ($n = 24$).

human frontal eye fields (FEFs; Paus 1996). Since activation maxima in left (goal hierarchy: –28 0 64; search depth: –28 –2 66) and right FEF (goal hierarchy: 30 4 62; search depth: 26 4 66) were closely overlapping, coordinates for VOI extraction were defined as the Euclidian centers of left (–28 –1 65) and right (28 4 64) activation peaks. By again taking the mean activation differences between conditions as dependent variable (Fig. 5B), an RM-ANOVA on side (left/right) and task parameter (goal hierarchy/search depth) revealed, however, neither main effects for side ($F_{1,23} = 0.39$, $P = 0.535$) and task parameter ($F_{1,23} = 0.90$, $P = 0.352$) nor an interaction between side and task parameter ($F_{1,23} = 0.01$, $P = 0.945$). That is, a double dissociation in terms of a crossover interaction between side and task demands could not be found for the bilateral FEF activations and appeared therefore to be specific for left and right dlPFC.

Lateralization Patterns on Single-Subject Level

Based on the preceding VOI analyses of the main effects of goal hierarchy and search depth, we further tested whether the confirmed pattern of a double dissociation for left and right dlPFC was also prevalent on the single-subject level by examining the frequencies and directions of hemispheric lateralization of task parameters for individual subjects. Results showed that a majority of 14 and 15 of the 24 subjects exhibited a predominant activation of left and right dlPFC for goal hierarchy and search depth, respectively. More specifically, only a single subject showed a pattern that entirely contrasted with the reported group results, while the full double dissociation pattern was evident in a cross section of a quarter of the subjects. Application of a McNemar test ($\chi^2_{(1)} = 6.33$, $P = 0.012$) confirmed that this frequency distribution differed significantly from chance.

Brain–Behavior Relationships

As already noted, the double dissociation may have been partly driven by the greater spatial extent of activation for goal hierarchy and search depth in left and right dlPFC, respectively. However, a greater spatial extent of activation does not necessarily imply a greater involvement in the cognitive function being tested. Brain–behavior relationships may be used to corroborate a more direct link between the strength of dlPFC activation and cognitive function. Therefore, we further addressed the putative relationships between the strength of the hemodynamic main effects for goal hierarchy and search depth in left and right dlPFC and the size of the respective main effects in behavioral latencies; that is, initial thinking and movement execution times. Structural equation modeling (SEM) was used to explore the covariation between the observed main effects in individual FIR time bins from 0 to 8 s capturing differences in the hemodynamic response (Fig. 4) and the observed differences in initial thinking times (Fig. 2).
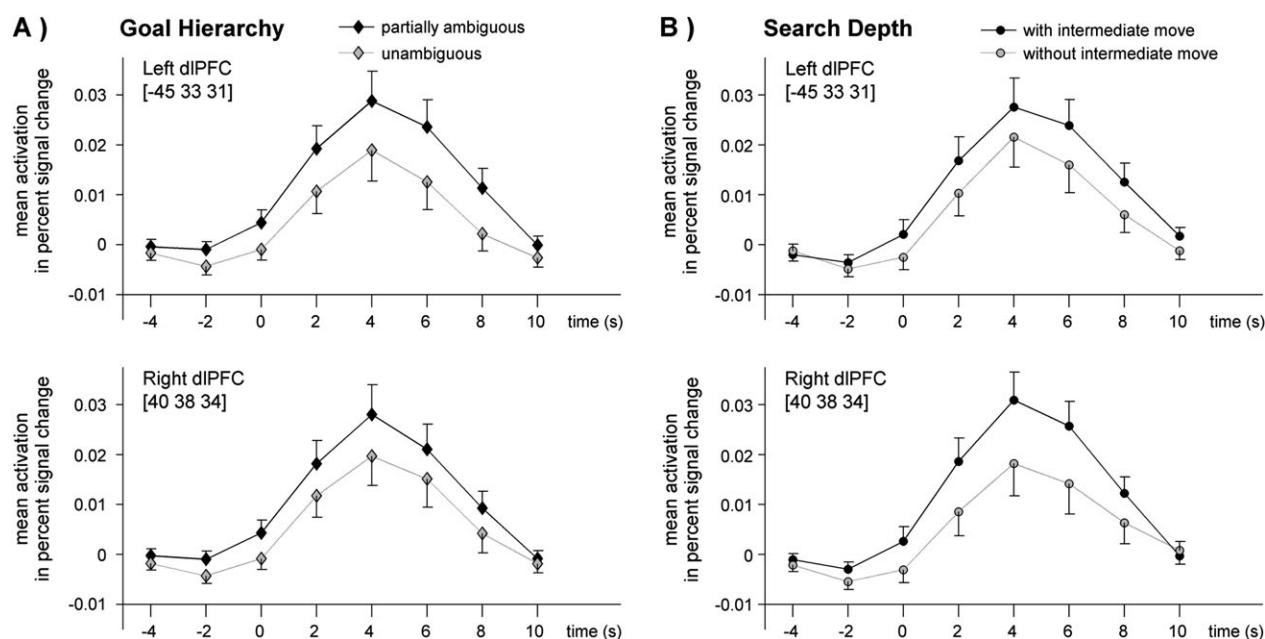
Table 3
Task-dependent activation of left and right dlPFC

Effect	Area	Cluster size	Coordinates			F value	P value (FWE)	P value (uncorrected)	z value
			x	y	z				
Goal hierarchy	Left dlPFC	169	−44	32	30	6.62	0.002	<0.0001	5.47
			−48	22	28	4.59	0.554	<0.0001	4.13
	Right dlPFC	27	42	40	34	5.00	0.223	<0.0001	4.43
Search Depth	Left dlPFC	38	−46	34	32	5.43	0.071	<0.0001	4.72
			−50	26	32	4.42	0.717	<0.0001	4.01
	Right dlPFC	194	38	36	34	6.01	0.013	<0.0001	5.10
			36	28	30	5.07	0.189	<0.0001	4.48
			48	40	26	4.35	0.788	<0.0001	3.95

Note: All reported activations passed a voxel-wise threshold of $P < 0.0001$ (uncorrected; $F > 4.05$) and exceeded an extension level of $k > 20$ voxels. Albeit still purely descriptive, data already imply a double dissociation between task parameters (goal hierarchy vs. search depth) and sides of predominant activation (left vs. right dlPFC) with respect to the strengths (z values) and extensions (cluster sizes) of the observed effects. In addition, a strong lateralization of dlPFC activations occurs when taking into account the statistical threshold of $P < 0.05$ (FWE corrected). In this case, goal hierarchy yields a left-lateralized dlPFC activation [−44 32 30], while search depth is associated with a right-lateralized dlPFC activation [38 36 34].

Figure 4. Main effects of (A) goal hierarchy and (B) search depth in left (top) and right dlPFC (bottom). Plots illustrate the time course of the hemodynamic response across FIR basis functions (i.e., time bins). Error bars indicate standard error of means.
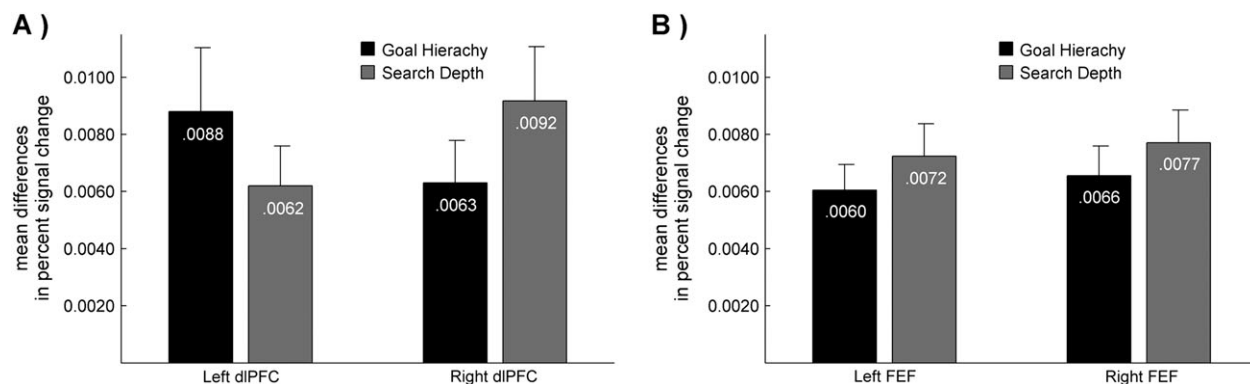
Figure 5. Mean differences in task-dependent activation for left and right dlPFC (*A*) and FEF (*B*). Bars illustrate the mean activation differences of the experimentally manipulated task parameters (goal hierarchy: partially vs. unambiguous; search depth: with vs. without an intermediate move). Numbers within panel provide means, and error bars indicate standard error of means.

In this respect, differential activations of left and right dlPFC were modeled as latent variables. Models were computed separately for goal hierarchy and search depth. Appropriate fit indices for SEM are being debated (Hair et al. 2006) and we thus report several assessments of how good the models reproduced the observed data. The χ^2 test provides evidence of adequate model fit with *P* values > 0.05 indicating no significant difference between the observed sample and the estimated covariance matrix. The χ^2/df ratio reflects the overall deviation of the empirical covariance matrix from the model-based estimation, divided by the degrees of freedom to account for the complexity of the model. A χ^2/df ratio <2 is commonly regarded as acceptable. Since this index is affected by sample size, the root mean square error of approximation (RMSEA) is therefore reported as a measure of the approximate model fit in the population. Lower RMSEA values indicate better fit, with values below 0.10 identifying adequate models (Hair et al. 2006).

Concerning brain–behavior relationships for initial thinking times, models for both goal hierarchy ($\chi^2_{(44)} = 37.70$, $P = 0.737$, χ^2/df = 0.857, RMSEA < 0.001) and search depth ($\chi^2_{(44)} = 51.93$, $P = 0.192$, χ^2/df = 1.18, RMSEA = 0.089) yielded acceptable fit indices. Most interestingly, behavioral main effects for goal hierarchy were mainly driven by the left dlPFC (Fig. 6*A*), whereas those for search depth were based on the contribution of the right dlPFC (Fig. 6*B*). That is, brain–behavior relationships assessed with SEM closely resembled the pattern of the double dissociation between task parameters and dlPFC lateralization as revealed by the preceding analyses. However, although the overall fit was acceptable for the 2 models, SEM on data sets with small sample sizes such as *n* = 24 have to be treated with caution.

Repeating the aforementioned SEM analyses for the latency effects in movement execution times as dependent variables did not reveal any estimable models due to nonexistent covariation with the observed effects in any of the individual time bins of the hemodynamic response, neither for left nor for right dlPFC.

Discussion

The dlPFC is assigned an important role in the anticipatory organization of action (Owen 2005; Tanji et al. 2007). Accordingly, previous studies on planning have mostly reported
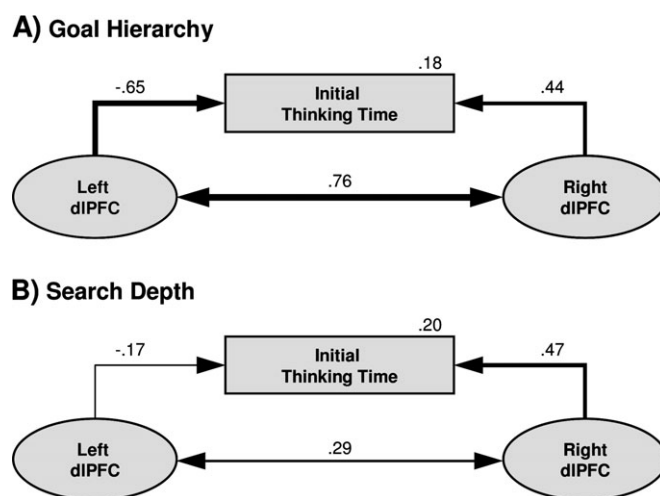

Figure 6. Brain–behavior relationships between main effects in dlPFC activation and initial thinking times for goal hierarchy (*A*) and search depth (*B*) as revealed by SEM. For both task parameters, hemodynamic activity of left and right dlPFC was modeled as latent variables based on the respective differential effects for time bins 3–7 (ranging from 0 to 8 s) and related to the manifest differences in initial thinking times. Manifest and latent variables are illustrated with boxes and circles, respectively. Standardized values are given for correlations between latent and manifest variables and for proportions of explained variance. Size of correlations is also reflected by thickness of arrows. A more detailed overview on the full models is provided in the Supplementary Fig. 4.

bilateral dlPFC activations (see Tables 1 and 2). These may be explained by 2 fundamentally different mechanisms: either 1) an unspecific recruitment of homologous areas across hemispheres due to resource-intensive processing or, alternatively, 2) simultaneous but specific contributions of left and right dlPFC to potentially separable task-related processes that in sum result in a bilateral activation pattern. In support of the latter assumption, we found in the present study a double dissociation in terms of a significant crossover interaction between the left and right dlPFC and 2 experimentally manipulated planning parameters, goal hierarchy and search depth. The often observed bilateral activations in complex tasks may hence reflect also a concomitant operation of specific cognitive processes that show opposing lateralizations.

Despite the high adaptivity of prefrontal neurons for representing a wide range of behavioral goals and means to

achieve them (Miller 2000; Miller and Cohen 2001), the present results demonstrate that there exists functional specialization between left and right dlPFC hence representing qualitative differences in information processing. Yet, the present double dissociation also provides clear evidence that—at least when observed macroscopically via fMRI—hemispheric specialization of the prefrontal cortex (Duncan and Owen 2000a; Duncan 2001; Duncan and Miller 2002) is not absolute: Experimental manipulations of the 2 task parameters resulted in functional changes on either side despite the observed emphases on task-dependent dlPFC lateralization (Fig. 5). That is, goal hierarchy led to stronger activation of left than right dlPFC, while search depth elicited stronger activation of right than left dlPFC, but in either case, neuronal assemblies in both hemispheres were recruited. Corroborating the observed double dissociation, the pattern of lateralized activation was found in a majority of single subject datasets. In addition, the double dissociation was shown to be specific for the dlPFC. Despite the presence of strong activation, no sign of lateralization was observed in the FEF or elsewhere in the prefrontal cortex. Finally, activation of left versus right dlPFC predicted the impact of planning parameters on initial thinking times.

Together, these results highlight the pivotal role of the dlPFC for planning. Extant theories of prefrontal cortex propose functional gradients of posterior to anterior regions, thereby reflecting increasingly abstract mechanisms of cognitive control (Koechlin and Summerfield 2007; Badre and D'Esposito 2009). In the framework of the cascade model, planning inherently implies high demands on episodic control since each individual problem configuration defines a novel set of rules for guiding action selection (Koechlin et al. 2003). That is, planning consistently requires updating the active task set to the restrictions imposed by the current situation. Considering the model proposed by Badre and D'Esposito (2007, 2009), planning can be thought of as dimensional integration or third-order relational processing, in that a start and a goal configuration, each defined by spatial relations between balls and pegs, have to be matched, thereby demanding the evaluation of relations (across states) among relations (within states). Both episodic control (Koechlin and Summerfield 2007) and dimensional integration (Badre and D'Esposito 2009) are proposed to be implemented via the dlPFC, as observed in the present study.

A theoretical foundation of lateralization of prefrontal function has been proposed by Wood and Grafman (2003) within the framework of structured event complexes (SECs). dlPFC is thought to store event sequences with left dlPFC being focused on specific features of individual events and right dlPFC mediating the integration of information across events (Huey et al. 2006). As a consequence, Grafman et al. (2005) proposed that "planning processes requiring the structural analysis of plans may be more compromised by left prefrontal lesions whereas the temporal and dynamic aspects of plans may be more compromised by right prefrontal lesions" (p. 191). The observed double dissociation between left and right dlPFC function in planning is hence consistent with the anatomical assumptions of the SEC framework (Grafman et al. 2005) as well as with other theoretical conceptions on the lateralization of dlPFC function (Shallice 2002).

In detail, goal hierarchy concerns the degree to which the sequence of the final goal moves can be deduced from the goal state (Klahr and Robinson 1981; Kaller et al. 2004). Unambiguous goal states provide an explicit order of the partial goals, that is, the sequence in which each ball has to be placed in its goal position can be completely derived from the goal state alone while not knowing anything about the start state. In partially ambiguous goal states, however, the order of the final goal moves can only be inferred by matching and integrating visuospatial information across the given start and goal configurations (Fig. 1). Yet, for the applied simple 3-move problems with an intermediate move, consideration of the start state may disambiguate partially ambiguous goal hierarchies (cf. Kaller et al. 2004). Hence, it is not the ability to derive the sequence per se that leads to increased initial thinking times in these problems but their identifiability from the goal state. That is, partially ambiguous goal states are associated with a higher demand on building up a mental representation of the encountered problem situation in terms of identifying, matching, and integrating relevant information pieces between start and goal states. This view is also supported by recent behavioral experiments using eye movement recordings showing that partially ambiguous goal hierarchies are related to an increased number of gaze alternations between start and goal state during the initial thinking time, whereas search depth and the need to accomplish an intermediate move was associated with substantially increased durations of the very last inspection of the start state before the beginning of the movement execution (K Nitschke, S Kappler, C Stahl, CP Kaller, unpublished data; see also Kaller et al. 2009).

In the present study, conforming with the view of Grafman et al. (2005) on left dlPFC function, cognitive processing in problems with an ambiguous goal hierarchy was associated with stronger activation of the left dlPFC that may reflect higher demands on structurally analyzing external information during planning. This interpretation is also in line with more general accounts that associate left dlPFC function with "sculpting" the response space, that is, generating a high-level task set incorporating the goals and rules of the task if these are not provided by the external context (Frith 2000; Shallice 2002). Although anatomically less specific, further support comes from Gazzaniga's (2000) proposal of a left hemispheric interpreter that attempts to assimilate perceived information into a comprehensible whole.

Concerning search depth, the results yielded a right lateralization of dlPFC activation. Conceptually, search depth is defined as the number of intermediate moves that must be considered before a first ball may be placed into its final goal position (Spitz et al. 1982; Kaller et al. 2004). Here, problems either did or did not require an intermediate move for optimal solution. While problems without an intermediate move can be solved by pure forward processing based on simple perceptual matching-to-sample strategies (Owen 2005; Kaller et al. 2008), the optimal solution in problems requiring an intermediate move can be achieved only by taking into account the interdependency between the individual steps. As depicted in Figure 1, moving away the obstructing ball at the outset can be accomplished by 2 move alternatives that are equivalent with regard to this initial aim (Kaller et al. 2008). However, only one of these 2 alternatives leads to an optimal solution, whereas the second choice would block the subsequent goal move and hence conflict with goal attainment.

Thus, the stronger right lateralization of dlPFC activation may be associated with increased demands for integrating
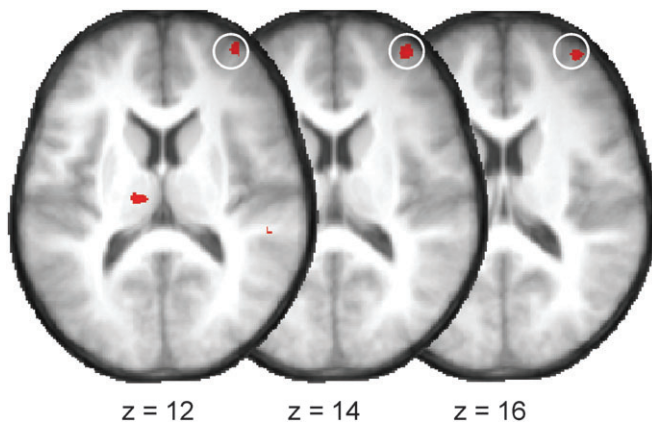
Figure 7. Activation of right aPFC (white circles) associated with higher demands on search depth (maximum peak at 36 54 14). Reported activations passed a marginally lowered voxel-wise threshold of $P < 0.0005$ (uncorrected; $F > 3.54$) and exceeded an extension level of $k > 20$ voxels. Applying the same threshold to the analysis of goal hierarchy did not yield contributions of the aPFC.

interdependent information into a coherent sequence (Grafman et al. 2005) in problems with intermediate moves. An alternative but closely related interpretation suggests that the larger involvement of the right dlPFC may be due to higher demands on monitoring and checking (Shallice 2002; Petrides 2005). Besides the evaluation and integration of information, the role of the right dlPFC in planning may also be associated with processes of path generation, that is, abilities to propose, develop, and temporally maintain move alternatives in the course of planning (Goel and Grafman 2000; Goel and Vartanian 2005; see also Burgess et al. 2000). Notably, in each step of planning in problems without an intermediate move, no move alternatives have to be generated since the next move can simply be determined by perceptually matching the current representations of start state and goal state (Owen 2005). The integration of interdependent information in problems requiring an intermediate move is also closely related to the theoretical concepts of subgoaling and branching control (Koechlin et al. 1999) since assessing different move alternatives concerning their consequences for subsequent moves requires temporarily maintaining the current state pending while move alternatives are processed (Koechlin and Summerfield 2007). Within prefrontal cortex, such coordination of information processing and transfer between multiple cognitive operations in the search of optimal behavior is attributed commonly to the anterior prefrontal cortex (aPFC; Ramnani and Owen 2004; Koechlin and Hyafil 2007). Although not of primary interest in the context of lateralization of dlPFC function, higher demands on search depth were associated with activation of the aPFC at a lowered threshold (Fig. 7), thus, again conforming with assumptions made on the rostrocaudal hierarchy of prefrontal function (Koechlin and Summerfield 2007).

In sum, the 2 experimentally manipulated problem parameters address conceptually different cognitive processes that were shown to be driven by dissociating activation patterns of left and right dlPFC. One should, however, note that the present independent manipulation of goal hierarchy and search depth apply to simple 3-move problems but may not be transferred directly to higher order problems. In particular, cognitive demands on ambiguous goal hierarchies in 5-move ToL problems compared with the applied 3-move problems

may in fact require higher demands on search processes and the generation of alternative move sequences (cf. McKinlay et al. 2008) and may thus potentially overlap with processes assigned here to the manipulation of search depth. That is, a "pure insertion" of specific demands is likely to be less straightforward in higher order problems.

In conclusion, our results suggest that the understanding of complex cognition may benefit from the identification and explicit manipulation of different task-related processes. As revealed for the dlPFC, bilateral brain activations may reflect separable cognitive functions that to some degree may even involve a hemispheric specialization at the highest, most abstract, and flexible levels of information processing in the human brain. While current conceptions of the functional organization of posterior to anterior frontal cortex (Koechlin and Summerfield 2007; Badre and D'Esposito 2009) have significantly enhanced our understanding of how complex demands are managed, the related experiments did not consider lateralization, and potential differences in function between the hemispheres had hence remained elusive. Our results conform with both these conceptions, assigning dlPFC a pivotal role for planning, and recent hypotheses of lateralized processing in the frontal lobes put forward by Grafman and colleagues (Wood and Grafman 2003; Grafman et al. 2005). Future studies should explicitly strive to combine the 2 views on frontal cortex, creating an integrated view of posterior to anterior and left to right functional specialization of function.

Supplementary Material

Supplementary material can be found at: http://www.cercor. oxfordjournals.org/.

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