NeuroImage 49 (2010) 2890–2900

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Differential role of anterior prefrontal and premotor cortex in the processing of relational information

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ARTICLE INFO

Article history:
Received 8 December 2008
Revised 16 August 2009
Accepted 12 September 2009
Available online 18 September 2009

ABSTRACT

Processing of relational information is a prerequisite underlying a number of higher cognitive faculties. Different brain regions within the frontal cortex have been implicated in supporting this function. The present study aimed at differentiating the roles of two frontal areas – anterior prefrontal cortex (aPFC) and premotor cortex (PMC) – in relational information processing using functional magnetic resonance imaging (fMRI). We tested the assumptions that PMC and aPFC differ as to their respective roles (1) in concrete (action-related) versus abstract relational information processing and (2) in concatenation versus integration of relational information. A reasoning paradigm adapted from Raven's Progressive Matrices was employed, manipulating the number and type of rules governing the matrices and creating an "abstract" and an "action" condition. Results suggest that PMC and aPFC are functionally differentiated by the type, not by the domain of relational processing, with PMC engaged in the sequential concatenation of relations, and aPFC in their integration. These results support hierarchical models of frontal function, while challenging the postulate of domain-specific processing within the frontal lobes.

Introduction

The acquisition and use of relational knowledge is central to a number of higher cognitive functions such as planning, problem solving, and reasoning. Relational knowledge is comprised of cognitive representations that include elements and relations between elements and that represent situations or activities in the world (Halford et al., 1998). Different parts of the frontal lobes, especially prefrontal (PFC) and premotor cortex (PMC), have been suggested relevant, but it remains unclear to what extent their functional roles are comparable or fundamentally different.

On one hand, PFC has been attributed the creation and maintenance of explicit relational representations that guide thought and action (Robin and Holyoak, 1995). Both neuropsychological (Waltz et al., 1999) and fMRI studies (e.g., Prabhakaran et al., 1997) further specified this concept by showing that PFC, especially its anterior portion (aPFC), is centrally involved in abstract tasks which require the integration of relations (Christoff et al., 2001; Kroger et al., 2002; cf. Ramnani and Owen, 2004).

On the other hand, PMC is involved in acquisition and planning of action sequences (Boussaoud, 2001; Kettner et al., 1996; Sakai et al., 2002). In particular, lateral PMC is suggested to hold precompiled subroutines or "action ideas" (Fadiga et al., 2000) which can be thought of as relational representations (e.g., between successive bodily postures or stages of object configurations) that guide action, whereas mesial PMC (supplementary motor area, SMA) selects and links these representations to make up higher-order actions (Shima and Tanji, 1998; Shima and Tanji, 2000).

Given these considerations, a first hypothesis about the roles of PMC and aPFC could be that the two areas differ with respect to the abstractness of the relational information processed, with aPFC and PMC processing relations in the cognitive and motor domains, respectively.

However, PMC is engaged in a wide range of highly abstract reasoning tasks (Acuna et al., 2002; Goel and Dolan, 2004; Knauff et al., 2003). It figures centrally in the processing of abstract stimulus sequences (Schubotz and von Cramon, 2001a; Schubotz and von Cramon, 2001b; Schubotz and von Cramon, 2002; overview in Schubotz and von Cramon, 2003). On the other hand, PMC is known to be involved in the acquisition and performance of action sequences (Harrington et al., 2000; Haslinger et al., 2002; Müller et al., 2002; Shima and Tanji, 1998; Shima and Tanji, 2000; Toni et al., 2001). It has hence been suggested that PMC serves as an interface which can be exploited for the representation of sequentially structured events in a broad range of behaviors including abstract cognitive tasks, and that relational processing in PMC could amount to the acquisition and application of transformations in both action and cognition (Schubotz, 2007).

Accordingly, a second hypothesis refers to the type of relational computations supported by PMC and aPFC rather than to the domain of

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1053-8119/$ – see front matter
doi:10.1016/j.neuroimage.2009.09.009

information processing. Thus, PMC could be recruited whenever sequential relations have to be generated or detected, but aPFC when several of such relations have to be integrated to make up higher-order relations.

The present study investigated to what extent the roles of aPFC and PMC are determined by the domain and by the level of relational information processing. To this end, we employed a paradigm adapted from Raven's Progressive Matrices (Raven, 1938). Matrices differed with regard to the stimulus material and to the number and type of rules they were governed by (for details, see Materials and methods). We expected aPFC to be activated by abstract rather than by action matrices, while the opposite should hold true for PMC. The aPFC should further show activation related to the number of rules, while PMC should be activated by matrices generated by sequential rules rather than by non-sequential ones.

Materials and methods

Subjects

Eight male and eight female university students (mean age, 26.4 years; range, 21–34 years) participated in the fMRI study. All participants provided written informed consent, and the study was conducted according to the guidelines of the ethics committee of the University of Leipzig. All subjects were right-handed as assessed using a German translation of the Edinburgh Handedness Inventory (Oldfield, 1971). None had any history of neurological or psychiatric illness, and all had normal or corrected-to-normal vision.

Experimental factors and anatomical hypotheses

The design corresponded to a balanced $2\times2\times2$ factorial design with factors Domain, Integration, and Type.

Firstly, the factor Domain was implemented by employing both an abstract version of the matrices task, in which stimuli were closely modelled on the original Raven's matrices, and a newly designed action version using photographs of simple object-directed hand actions as stimulus material. In the abstract version, rules to be inferred and applied to solve the matrices concerned visuospatial relations between elements of abstract graphical images, whereas in the action version, rules concerned real objects and the way they were manually manipulated. According to the first hypothesis tested, PMC should be activated by action matrices rather than by abstract ones, whereas the opposite should be true for aPFC.

The factor Type was implemented by employing two different types of rules, one requiring sequential processing of stimuli (Raven's matrices rule “Quantitative pairwise progression”; “sequential” hereafter) the other non-sequential processing (Raven's matrices rule “Distribution of three values”; “distributive” hereafter) (Carpenter et al., 1990). The sequential rule consists in the repeated application of one single transformation command within matrix rows (e.g., “add one more item”) and entails a strict sequential

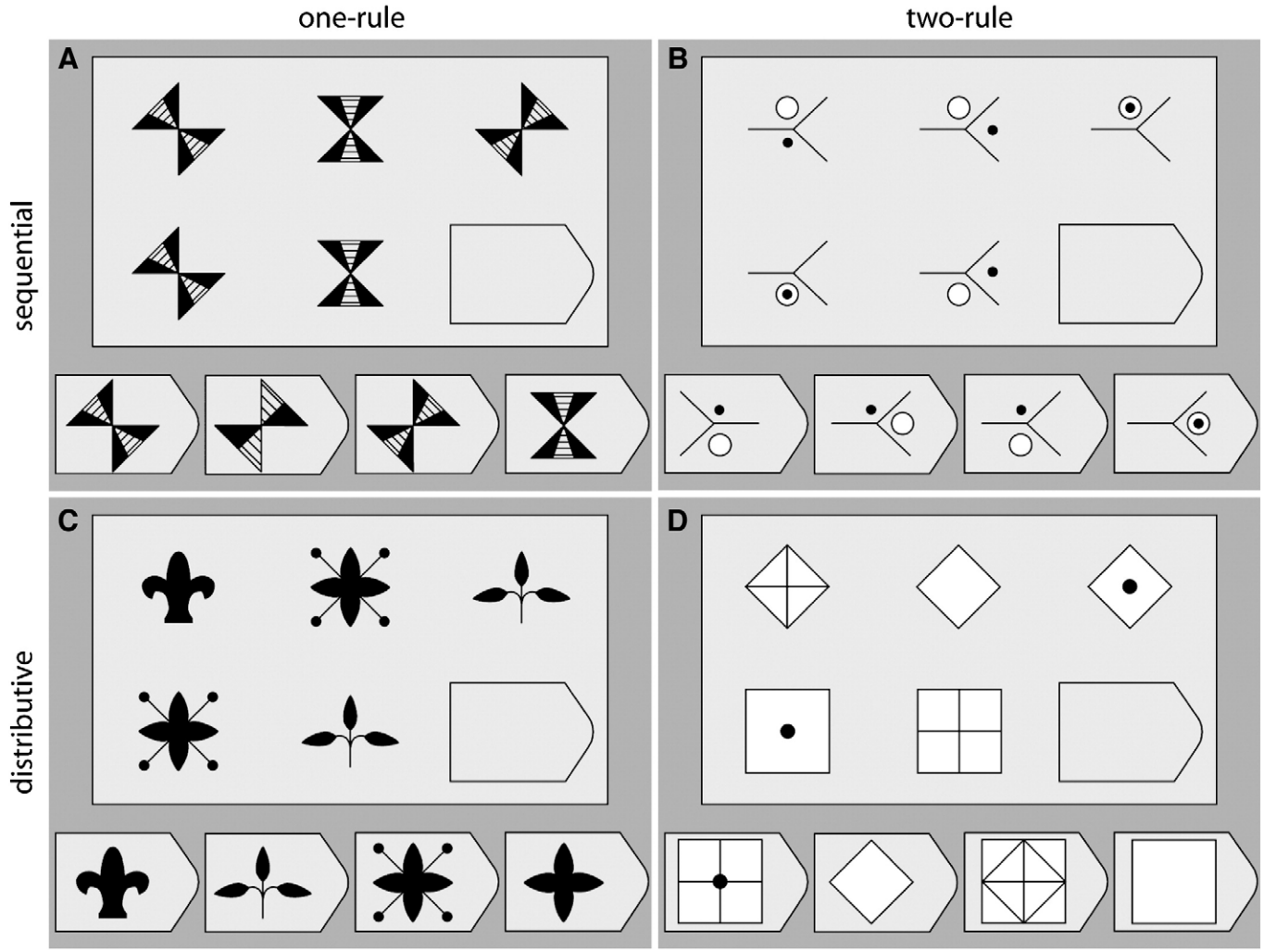

Fig. 1. Example matrices in the abstract domain: (A) one-rule/sequential, (B) two-rule/sequential, (C) one-rule/distributive, and (D) two-rule/distributive conditions. The correct answers are (alternative from left) third (A), third (B), first (C), and fourth (D).

progression from the right to the left entry of the matrix (or vice versa). In contrast, the distributive rule amounts to the application of three transformation commands that differed within matrix rows (horizontally) but amounted to the same set between matrix rows (vertically). Thus, these matrices did not prescribe any specific progression or order of rule applications. According to the second hypothesis, PMC was expected to be active in matrices generated by sequential rules rather than by non-sequential ones.

Regarding the third and orthogonal factor Integration, each matrix was governed either by one rule or by a combination of two rules. According to the literature, we expected activation in aPFC, but not in PMC, to be elevated by the requirement to process two-rule as compared to one-rule matrices, since the former, in contrast to the latter, require relational integration (Christoff et al., 2001; Kroger et al., 2002).

Stimuli and task

Stimuli were modelled on the Raven's Progressive Matrices (Raven, 1938). In the upper part of each stimulus display, five individual stimuli (graphical images or photographs) and a wildcard – always in the lower right position – formed a 3×2 matrix. Below the matrix, four slightly smaller stimuli were presented as answer alternatives.

The subjects' task was to find the graphical image or photograph that would complete the matrix correctly. Subjects were made aware that for each matrix problem there was one and only one correct solution.

Matrices were constructed by the combination of three factors, as delineated above.

Factor Domain: In abstract problems, stimuli were abstract, black-and-white graphical images that resembled the stimuli used in the original Raven's matrices. In action problems, stimuli were black-and-white photographs of simple hand actions performed on small everyday objects.

Factor Integration: One-rule and two-rule matrices were presented. One-rule matrices were governed by a single rule. In contrast, two-rule matrices were governed by two rules that had to be considered simultaneously to determine the correct solution, thus requiring integration of relations.

Factor Type: Rules of the types described in the analysis of Carpenter et al. (1990) were used in the construction of the matrices. The rule governing a one-rule matrix, regardless of domain, could be either "constant in a row but changing down a column", "quantitative pairwise progression" (sequential), or "distribution of three values" (distributive). Rule combinations governing the two-rule matrices were the sequential rule combined with itself or with the "constant in a row" rule, or else the distributive rule combined with itself or with the "constant in a row" rule. The "constant in a row" rule was included to ensure variation in the systematics of the matrices, and the rule combinations were chosen to guarantee an equal proportion of matrices governed by the different rule types. The same rule combinations were used in the abstract and in the action conditions.

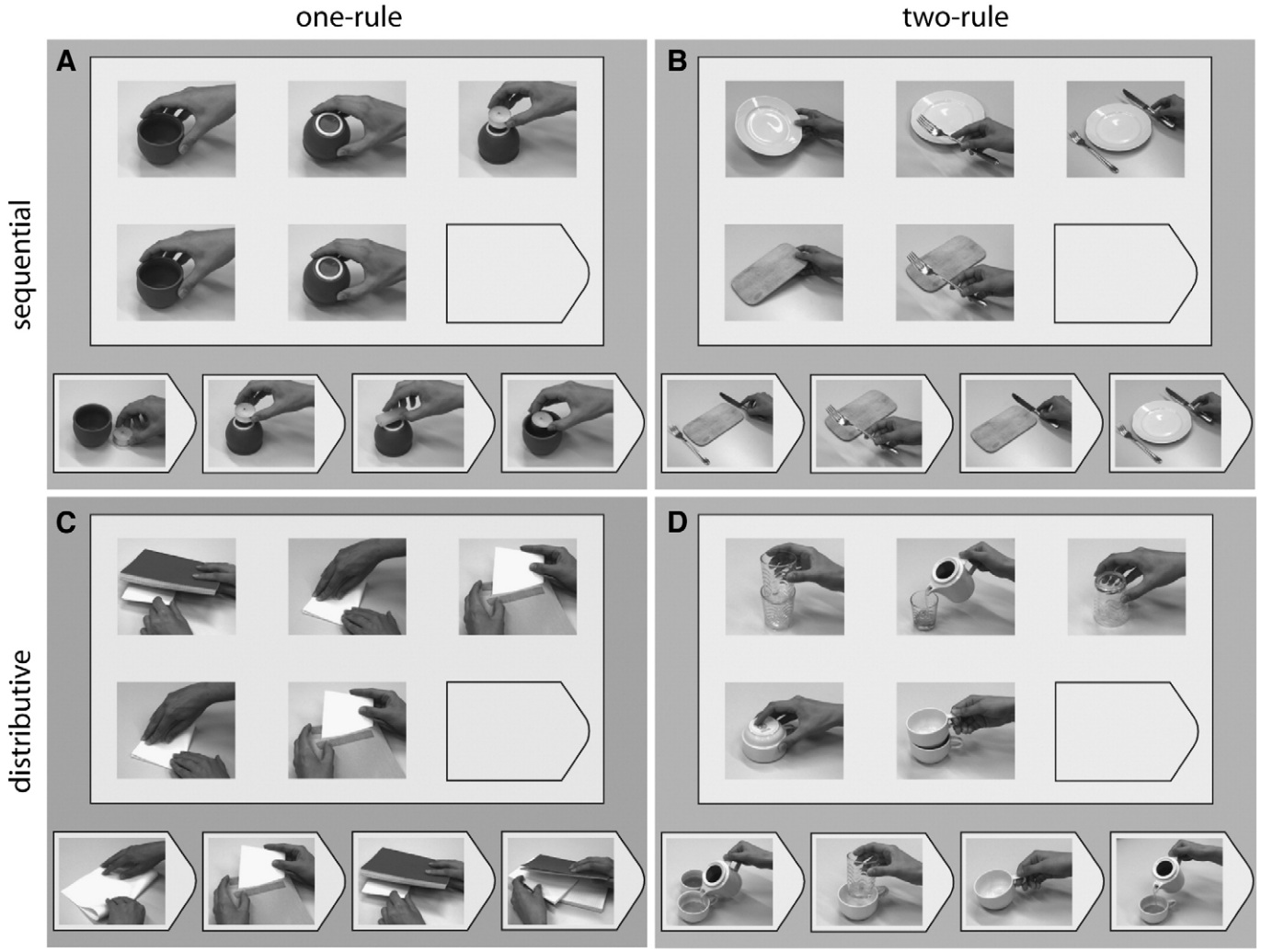

Fig. 2. Example matrices in the action domain: (A) one-rule/sequential, (B) two-rule/sequential, (C) one-rule/distributive, and (D) two-rule/distributive conditions. The correct answers are (from left) second (A), first (B), third (C), and fourth (D).

Examples for abstract and action matrix problems constructed following the different rules are given in Figs. 1 and 2. In Fig. 1, abstract matrices are presented, each corresponding to a combination of levels of the two other factors Integration and Type. In Fig. 2, analogous action matrices are presented.

Behavioral procedure

A total of 96 matrices were presented, corresponding to 96 experimental trials. Matrices were presented in a pseudo-randomized fashion with a different order for every subject, interspersed randomly with an additional 20 baseline trials in which a blank screen was shown for 15 s. An experimental trial started with a fixation cross presented in the middle of the screen for 1000 ms, followed by the presentation of the stimulus display which remained on the screen until the subject's response, but for a maximum of 25 s. The response was to be indicated by pressing the keyboard button spatially corresponding to the selected alternative, with one of the four fingers of the right hand. Response time (RT) was measured as the time from problem onset to button press. Following their response, subjects received a correctness feedback, and the next trial started after a variable delay of 4000–5000 ms.

The instructions stressed accuracy over speed. Immediately before scanning, subjects completed a brief training session outside the scanner, solving one problem of each domain and rule or rule combination.

Imaging procedure

MRI scanning was performed on a 3-T Siemens Trio scanner (Siemens, Erlangen, Germany). Functional images were obtained using a gradient-echo EPI sequence (TE = 30 ms, flip angle = 90°, TR = 2000 ms). Twenty-four axial slices with a thickness of 4 mm and an interslice gap of 1 mm (FOV = 19.2 cm, 64 × 64 matrix, in-plane resolution 3 × 3 mm) were acquired parallel to the AC–PC line. During scanning, subjects viewed the screen via a head-mounted visual stimulation device and had the four fingers of their right hand positioned on the response buttons.

Immediately before the functional experiment, a set of two-dimensional anatomical images was acquired using an MDEFT sequence (Norris, 2000; Ugurbil et al., 1993). In addition, high-resolution whole-brain images (160 slices, 1-mm thickness) were acquired for each subject in a separate session and subsequently standardized to Talairach stereotactic space (Talairach and Tournoux, 1988) to provide an individual 3D reference data set.

Imaging data analysis

Analysis of MRI data was carried out using the software package LIPSIA (Lohmann et al., 2001). Functional data were motion corrected offline with the Siemens motion correction protocol. To correct for the temporal offset between the slices acquired in one scan, a cubic-spline interpolation was applied. Slice gaps were then interpolated to generate output data with a spatial resolution of 3 × 3 × 3 mm.

To align the functional data slices with a 3D stereotactic coordinate reference system, a rigid linear registration with six degrees of freedom (three rotational, three translational) was performed. The rotational and translational parameters were acquired on the basis of the MDEFT slices and subsequently transformed by linear scaling to a standard size to achieve an optimal match between these slices and the individual 3D reference data set. The resulting parameters were then used to transform the functional slices using trilinear interpolation, so that the resulting functional slices were aligned with the stereotactic coordinate system. A temporal high-pass filter with a cutoff frequency of 1/130 Hz was used for baseline correction of the signal, and the data were spatially smoothed using a 3D Gaussian kernel of 5 mm FWHM.

The statistical evaluation was based on a least-squares estimation using the general linear model for serially autocorrelated observations (Friston, 1994; Friston et al., 1995a; Friston et al., 1995b; Worsley and Friston, 1995). Only correctly answered trials entered the analysis. Error trials were modelled as a single separate condition but not analyzed. Given the potential for very long events, and to account for RT differences between trials, the duration of the individual events in the model was adjusted to match the response time on each trial. Furthermore, to account for activation differences which are simply due to time on task, RT was modelled as an extra regressor (variable of no interest). The event-related design matrix was generated with a synthetic hemodynamic response function (Friston et al., 1998; Josephs et al., 1997). The model equation, including the observation data, the design matrix, and the error term, was convolved with a Gaussian kernel of dispersion of 4 s FWHM to deal with the temporal autocorrelation (Worsley and Friston, 1995).

In the following, contrast images, i.e., parameter estimates of the raw-score differences between specified conditions, were generated for each subject. The single-subject contrast images were then entered into a second-level random effects analysis for each of the contrasts, consisting of a one-sample *t*-test across the contrast images of all subjects that indicated whether observed differences between conditions were significantly distinct from zero (Holmes and Friston, 1998). Subsequently, *t*-values were transformed into *Z*-scores. To ensure that only activations but not deactivations relative to baseline are reported, contrasts were masked with a contrast of all experimental conditions versus baseline. Multiple comparison correction was performed by employing a combination of individual voxel probability thresholding and minimum cluster-size thresholding, whereby the uncorrected probability threshold was set to $p = .001$ and the cluster-size threshold was computed using Monte-Carlo

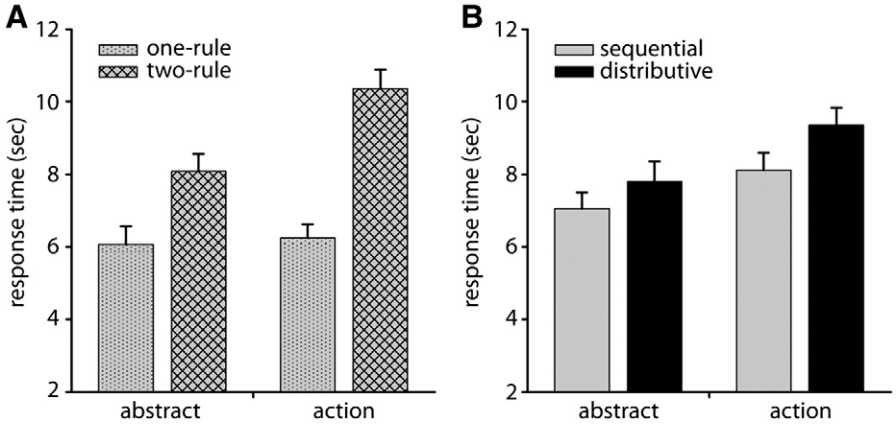

Fig. 3. Effects of (A) domain and requirement for relational integration and (B) domain and rule type on response time (RT).

simulations (Forman et al., 1995; Xiong et al., 1995). This procedure resulted in a minimum size of 459 mm^3 for clusters of activation to be reported at a significance level of $p<.05$ (corrected).

The whole-brain analyses were complemented by region of interest (ROI) analyses. ROIs were defined as described in the Results section. For each condition and subject, parameter estimates were averaged across all voxels of an ROI and subsequently entered into repeated measures ANOVAs.

Results

Behavioral performance

Participants' mean response time (RT) across all conditions was 7.60 s (SE 0.43). The effects of the factors domain (abstract, action) and integration (one-rule, two-rule) on RT data were analyzed using a two-way repeated measures ANOVA. As expected, two-rule matrices took longer to solve than one-rule matrices ($F(1,15)=164.75$, $p<.001$). Action matrices were solved slower than abstract matrices ($F(1,15)=19.42$, $p<.01$), and there was a significant interaction ($F(1,15)=46.60$, $p<.001$) indicating that the RT difference between two-rule and one-rule matrices was higher in the action than in the abstract domain (Fig. 3A).

A second two-way ANOVA was conducted to determine the effect of rule type (sequential, distributive) on RT, again including the factor domain. As shown in the previous analysis, RT was longer for action than for abstract matrices ($F(1,15)=18.91$, $p<.01$). RT was also longer for matrices containing the distributive rule than for matrices containing the sequential rule ($F(1,15)=46.15$, $p<.001$); however, the interaction effect was not significant (Fig. 3B).

The overall error rate was low ($M=5.53$ %, SE $=0.99$). Analogous to the RT analysis, a two-way repeated measures ANOVA showed that two-rule matrices, in addition to taking longer to solve, also elicited more errors than one-rule matrices ($F(1,15)=24.41$, $p<.001$). Error rates did not differ between domains, and there was no interaction (Fig. 4A). The ANOVA testing the effects of domain and rule type on error rates found no difference between problems governed by the sequential or the distributive rule but a significant interaction ($F(1,15)=6.32$, $p<.05$) as illustrated by Fig. 4B.

Note that although this was a $2\times2\times2$ design, we did not employ a three-way ANOVA for two reasons. Firstly, we did not have any hypotheses regarding the three-way interactions. In addition, in case of the error rate as the dependent variable, the data did not fulfill the requirement for performing the three-way ANOVA (normal or near-normal distribution within the cells of the design) due to the fact that most subjects made very few errors. However, the data fulfilled the requirement for the two separate two-way ANOVAs. For clarity, we performed analogous analyses on the error rate and response time data.

Imaging results

In order to analyze which brain regions are involved in relational processing in each of the two domains, the main effect of domain was examined. Fig. 5A shows the contrast of action matrices versus abstract matrices (red) and the reverse contrast, abstract versus action matrices (blue), collapsed across factors integration and rule type. Areas activated in these contrasts are detailed in Table 1. The analyses revealed that action matrices compared to abstract matrices elicited bilateral activations in a number of brain regions. Most prominently, activation in the lateral occipito-temporal cortex extended from the middle occipital gyrus into the posterior parts of the middle and superior temporal gyri and the superior temporal sulcus. Clusters of activation were also present in the fusiform gyri and in the middle part of the inferior frontal sulci in both hemispheres. The reverse contrast, abstract compared to action matrices, yielded clusters of activation in the cuneus and inferior parietal lobules bilaterally as well as in the right posterior intraparietal sulcus and right cerebellar hemisphere. No activation was apparent in either anterior prefrontal or premotor cortex. As a caveat, it is worth keeping in mind that there was a descriptive, albeit statistically nonsignificant difference in accuracy between the action and the abstract condition.

Since in solving the two-rule matrices, substantially more reasoning was required than in the one-rule matrices, and there was a significant domain by integration interaction regarding RT, we also computed the contrasts between action and abstract matrices specifically for the two-rule conditions. However, the resulting activations were largely comparable to the collapsed condition (Fig. 5). Importantly, no additional clusters of activation emerged in either aPFC or PMC for this analysis compared to when collapsing across one-rule and two-rule trials.

Brain regions recruited for integration of relations were determined by computing the two-rule matrices versus one-rule matrices contrast. The resulting map is displayed in Fig. 6, details on clusters of activation are given in Table 2. A network of primarily frontal and parietal areas was evident. Frontal activations were pronounced in the left hemisphere. They encompassed the posterior part of the medial and lateral superior frontal gyrus, the precentral sulcus, extending anteriorly along the inferior frontal sulcus with extensive activation in the adjacent middle and inferior frontal gyri into the lateral part of the frontopolar cortex. Activation was also apparent in the left anterior insula, right posterior superior frontal sulcus, and middle frontal gyrus. In addition, relational integration elicited extensive activation in the precuneus and the superior and inferior parietal lobules in both

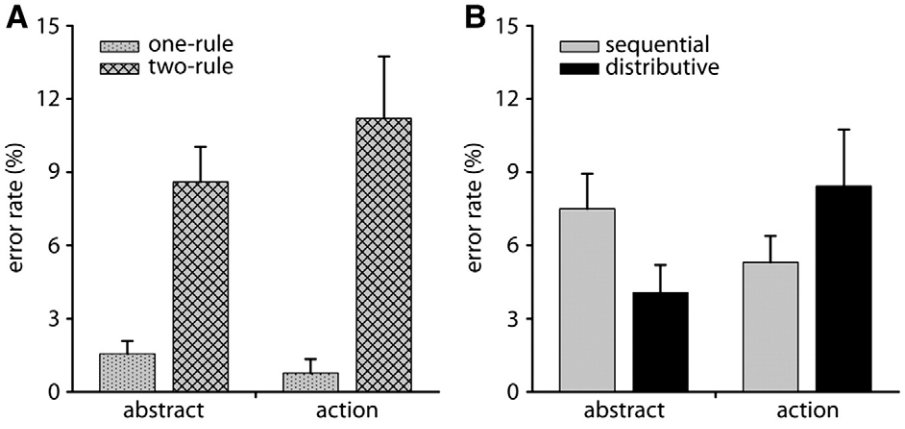

Fig. 4. Effects of (A) domain and requirement for relational integration and (B) domain and rule type on error rates.

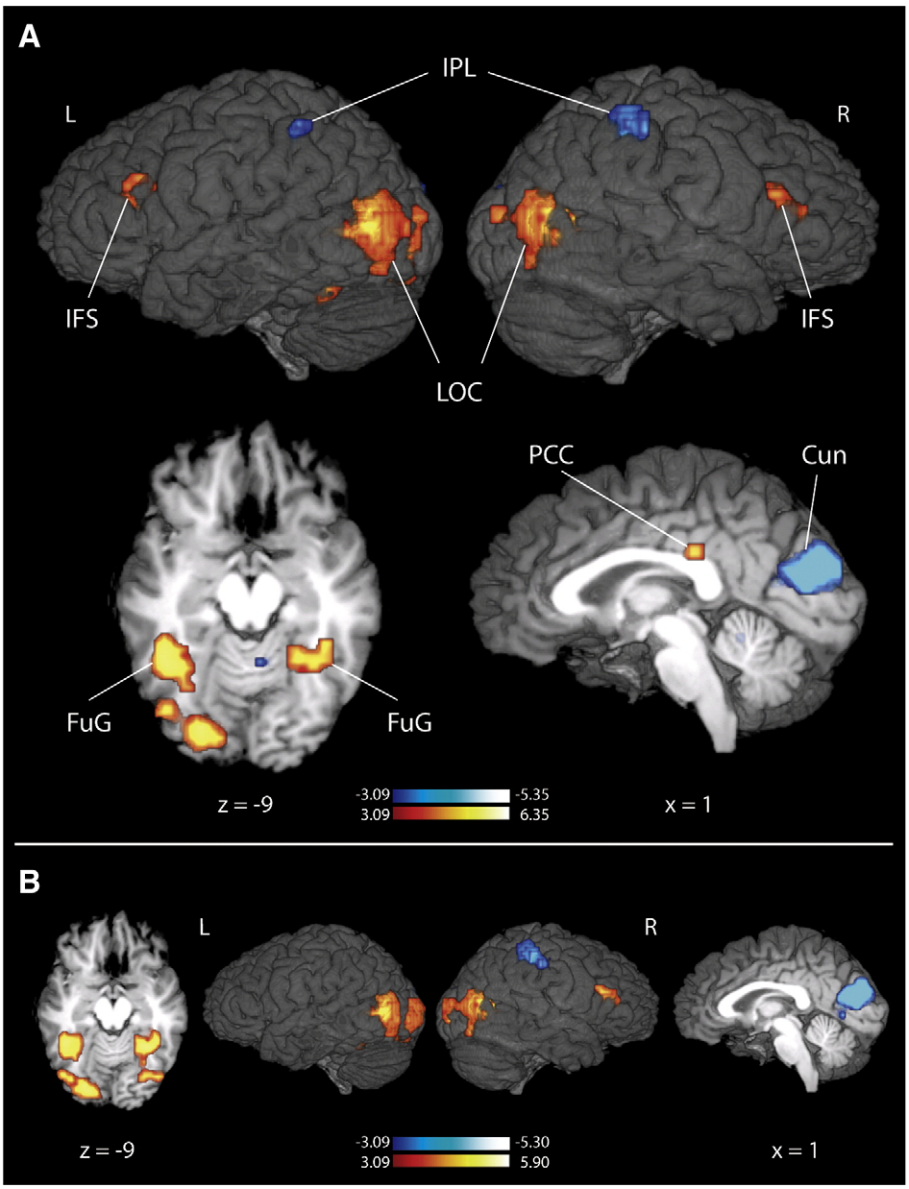

Fig. 5. Brain correlates of domain of relational processing. Brain areas significantly activated in the action>abstract contrast are displayed in red, activations in the reverse contrast abstract>action are displayed in blue. (A) For both contrasts, trials were collapsed across factors integration and rule type. (B) The same contrasts for the two-rule trials only, collapsed across rule type. Group-averaged *Z*-maps ($n = 16$) are overlaid onto an individual subject anatomical image ($p < .05$, corrected).

Table 1
Anatomical specification, hemisphere, mean Talairach coordinates (*x*,*y*,*z*), volume (in mm^3), and maximal *Z*-scores of significantly activated clusters for the contrast of action versus abstract matrices and the contrast of abstract versus action matrices.

Area		*x*	*y*	*z*	mm^3	Z_{max}
Action vs. abstract						
Posterolateral temporal cortex/lateral occipital cortex (LOC)	L	−53	−70	9	11907	6.35
Posterolateral temporal cortex/lateral occipital cortex	R	43	−67	12	8478	5.56
Fusiform gyrus (FuG)	L	−41	−43	−9	2970	4.46
Fusiform gyrus	R	25	−49	−12	1674	3.96
Inferior frontal sulcus (IFS)	L	−41	17	18	918	3.94
Inferior frontal sulcus	R	46	29	12	810	4.14
Posterior cingulate cortex (PCC)	L	−5	−31	30	459	3.79
Abstract vs. action						
Cuneus (Cun)	R/L	4	−82	21	8964	5.36
Inferior parietal lobule (IPL)	L	−41	−40	39	459	4.09
Inferior parietal lobule	R	43	−37	42	1998	4.63
Posterior intraparietal sulcus	R	19	−70	39	459	3.70
Cerebellar hemisphere (Ce)	R	10	−52	−18	837	4.09

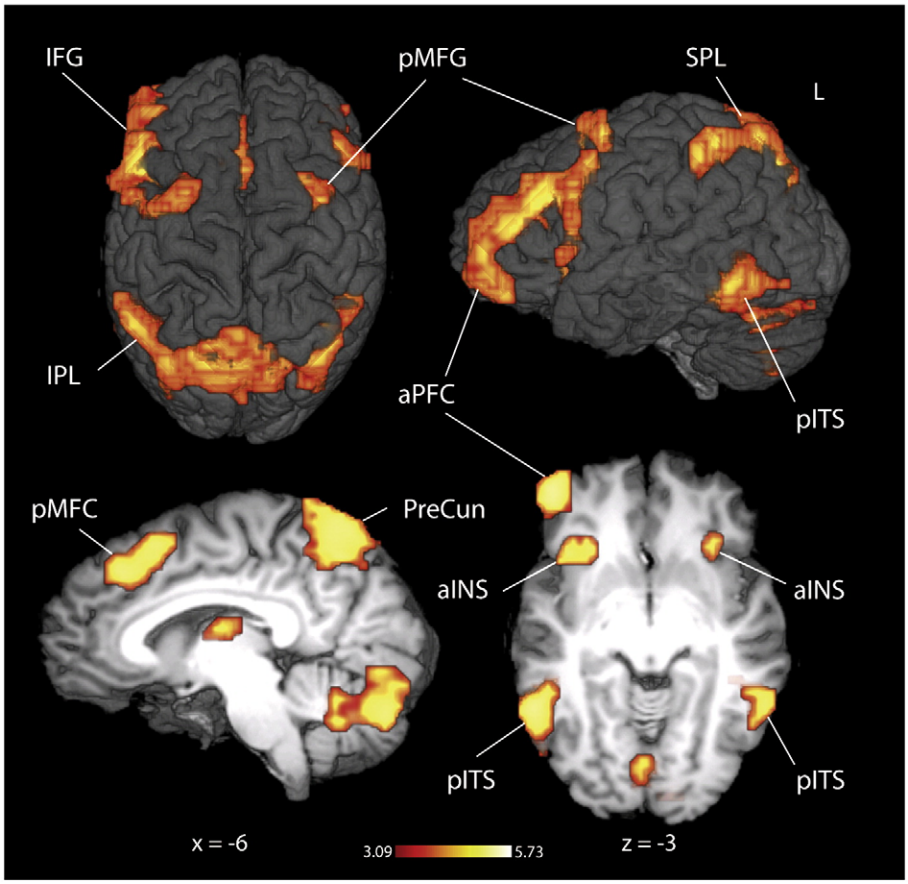

Fig. 6. Brain correlates of requirement for integration. Two-rule>one-rule contrast, collapsed across factors domain and rule type.

hemispheres as well as some activation bilaterally in posterior inferior temporal sulcus and in the cerebellar hemispheres.

In order to assess activation patterns related to the rule type manipulation, the BOLD signal was averaged over all trials containing the sequential rule and all trials containing the distributive rule, respectively. Since no matrices were presented that contained both of these rules, the two conditions were mutually exclusive. The contrasts of distributive rule matrices versus sequential rule matrices and vice versa were computed. The resulting activations are listed in Table 3 and illustrated in Fig. 7. In view of our target regions PMC and aPFC, a prominent cluster of activation in the right ventrolateral PMC was found, in which BOLD response was higher for sequential rule matrices than for distributive rule matrices. This pattern was also observed for two regions in the right inferior parietal lobule and the posterior part of the right middle temporal gyrus, respectively. Only one cluster of activation emerged in the contrast of distributive rule matrices versus sequential rule matrices, this cluster encompassing the superior part of the precuneus and cuneus in the left hemisphere. Furthermore, the results of the behavioral analyses displayed in Figs. 3B and 4B indicate that performance of the action but not the abstract trials benefits from the ability to draw on knowledge about sequences of actions. We therefore also computed the contrast of the sequential versus distributive matrices specifically for the action condition. However, no additional regions of activation emerged. In the reverse contrast, distributive versus sequential matrices, one additional cluster of activation was apparent in the

Table 2
Anatomical specification, hemisphere, mean Talairach coordinates (*x*,*y*,*z*), volume (in mm^3), and maximal *Z*-scores of significantly activated clusters for the contrast of two-rule versus one-rule matrices.

Area		*x*	*y*	*z*	mm^3	Z_{max}
Two-rule vs. one-rule						
Posterior middle frontal gyrus (pMFG), inferior (IFG) and middle frontal gyrus, posterior mediofrontal cortex (pMFC), anterior insula (aINS)	L	−32	2	51	27405	5.74
Posterior middle frontal gyrus	R	22	8	42	2052	4.57
Middle frontal gyrus, precentral sulcus	R	34	11	24	6858	4.47
Inferior and superior parietal lobule (IPL/SPL), precuneus (PreCun)	L	−47	−46	45	23139	5.72
Inferior parietal lobule	R	31	−73	39	7587	5.09
Posterior inferior temporal sulcus (pITS)	L	−53	−52	−6	6885	5.26
Posterior inferior temporal sulcus	R	49	−46	−9	1890	4.02
Globus pallidus	L	−17	−10	18	1620	4.17
Cerebellar hemisphere	R	28	−70	−30	18333	5.16

Table 3
Anatomical specification, hemisphere, mean Talairach coordinates (*x*,*y*,*z*), volume (in mm^3), and maximal *Z*-scores of significantly activated clusters for the contrast of distributive versus sequential rule matrices and the contrast of sequential versus distributive rule matrices.

Area		*x*	*y*	*z*	mm^3	Z_{max}
Distributive vs. sequential						
Cuneus, precuneus	L	−8	−88	33	4833	4.50
Sequential vs. distributive						
Premotor cortex (PMC)	R	43	5	33	1755	4.00
Inferior parietal lobule	R	49	−31	42	5670	4.65
Posterior middle temporal gyrus (pMTG)	R	40	−58	3	810	4.22

right cerebellar hemisphere ($x = 34$, $y = -55$, $z = -24$, 864 mm^3, $Z_{max} = 3.60$).

The whole-brain analyses showed no evidence for a main effect of domain in either anterior prefrontal cortex or premotor cortex. As predicted, aPFC showed only a main effect of integration while PMC showed only a main effect of rule type.

ROI analyses were then conducted in order to (1) confirm the whole-brain findings, (2) examine the effects of the other factors in each ROI, and (3) provide statistics for the ROI × effect interactions postulated.

In order to avoid a biased analysis as discussed in recent literature (cf. Kriegeskorte et al., 2009), ROIs were not defined from the respective whole-brain contrasts, but specified as follows. In PMC and aPFC, we first selected Talairach coordinates of maxima reported in relevant studies and contrasts. For PMC, we chose a cluster of activation apparent when sequential information about the object properties of an abstract sequence had to be processed in contrast to a control condition where no sequential information had to be processed (maximal *z*-value reported at Talairach coordinates 34 6 32; Schubotz and von Cramon, 2001a). For aPFC, we chose a cluster of activation apparent when two-relational matrix problems were compared to one-relational problems (maximal *z*-value reported at Talairach coordinates −34 50 9; Christoff et al., 2001). In each case, we then determined the Talairach coordinates of the nearest local maximum in the contrast of all experimental conditions against baseline of our experiment in order to ensure that we do not select ROIs that show a deactivation relative to baseline. For the PMC, this maximum was at Talairach coordinates 34 3 30, for the aPFC at −44 39 21. Finally, we created spherical ROIs with a diameter of 6 mm around these coordinates.

A four-way repeated measures ANOVA with factors ROI (aPFC/PMC), domain, integration, and rule type was then performed on the parameter estimates. Of interest in this analysis were primarily the interactions of ROI with the other factors. The ROI × integration interaction ($F(1,15) = 23.99$, $p < .001$) and the ROI × rule type interaction ($F(1,15) = 18.68$, $p < .01$) proved to be significant. The ROI × domain interaction was not significant, and neither was any other interaction containing the factor ROI.

Subsequently, three-way ANOVAs with factors domain, integration, and rule type were conducted separately in each ROI. In aPFC, BOLD response was higher for two-rule than for one-rule matrices ($F(1,15) = 33.71$, $p < .001$), as suggested by the whole-brain contrast. No other main effects or interactions were significant. Paired *t*-tests confirmed that BOLD response in aPFC was elevated for two-rule in comparison to one-rule matrices in the abstract ($t(15) = 3.57$, $p < .01$) and the action domain ($t(15) = 5.71$, $p < .001$) (Fig. 8A). In contrast to the aPFC ROI, in PMC there was a significant main effect of rule type confirming that BOLD response in this region was higher for sequential than for distributive rule matrices ($F(1,15) = 8.62$, $p < .05$). Again, no other main effects or interactions were significant. Paired *t*-tests showed that in PMC, BOLD response was higher for sequential as compared to distributive rule matrices both in the abstract ($t(15) = 2.36$, $p < .05$) and the action conditions ($t(15) = 2.35$, $p < .05$) (Fig. 8B). In summary, the ROI analyses well-corroborated and substantiated the results from the whole-brain contrasts.

Discussion

The present fMRI experiment investigated the roles of two frontal lobe regions – premotor cortex (PMC) and anterior prefrontal cortex (aPFC) – in relational processing. Specifically, we focused on two potential factors as determinants of PMC and aPFC involvement, namely, on the processing domain, considering action-related versus abstract relational processing, and on the type of relational processing, considering processing of sequential relations versus relational integration.

Data replicated prior imaging studies' findings on relational integration in abstract matrices tasks (Kroger et al., 2002; Prabhakaran et al., 1997). In line with these previous accounts, we conceived relational integration as the simultaneous consideration of several relations between matrix entries. In this conceptualization, integration does not just entail the actual step of inserting the results of the current subtask into a stored representation but also includes the maintenance of these representations during periods of subtask processing (De Pisapia et al., 2007). The present results confirm that a widespread bilateral fronto-parietal network is recruited for relational integration. Concerning our two target areas, left aPFC was found to be included in this network. There was no activity in lateral PMC; however, medial frontal activation extended into the pre-SMA, although without reaching a local maximum there. While extended lateral prefrontal areas were activated as well, this activity merely bordered the precentral gyrus without reaching the gyral surface. Accordingly, aPFC but not lateral PMC can be considered significantly enhanced by relational integration. Strikingly, this data pattern was independent of

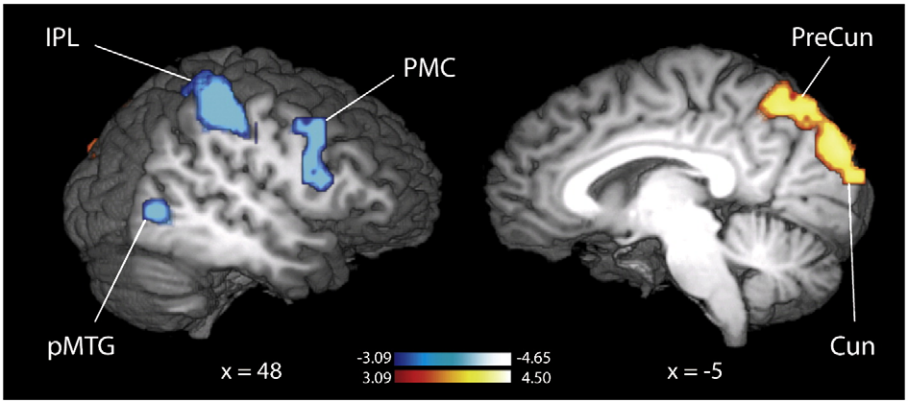

Fig. 7. Brain correlates of rule type manipulation. The contrast of distributive > sequential rule matrices is displayed in red, the reverse contrast sequential > distributive in blue. For both contrasts, trials were collapsed across factors domain and integration.

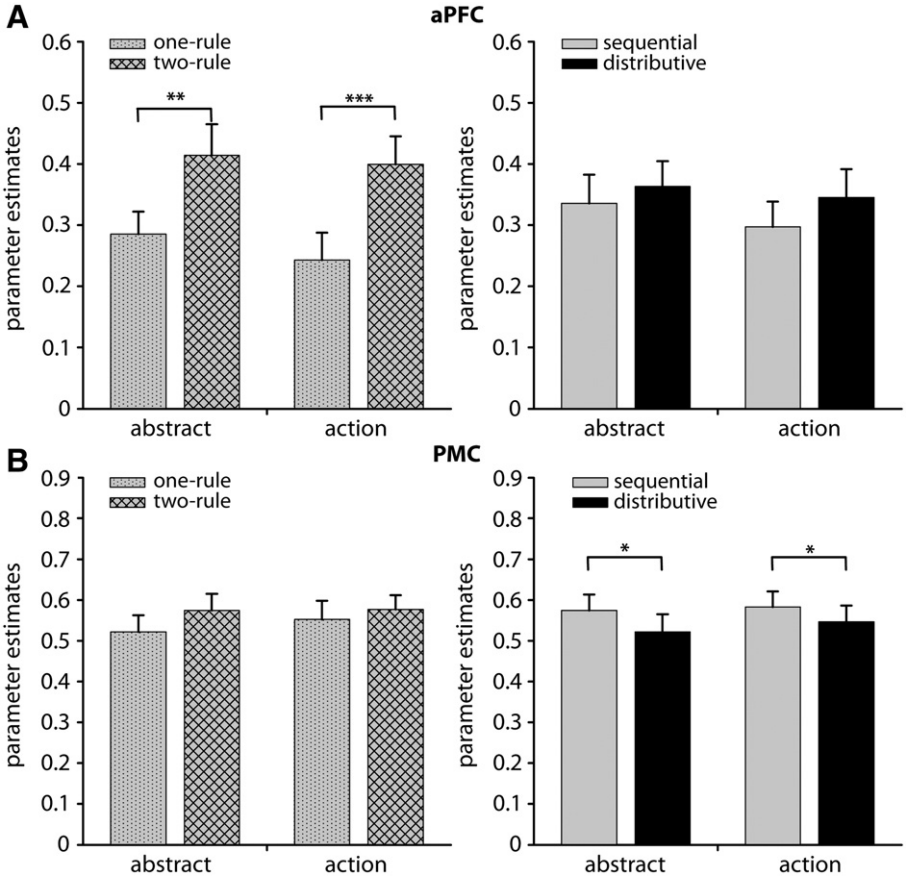

Fig. 8. Results of ROI analyses. (A) Effects of requirement for relational integration and rule type on BOLD response in aPFC. (B) Effects of requirement for relational integration and rule type in PMC. ***$p < .001$ **$p < .01$ *$p < .05$.

the informational domain, i.e., both areas were found engaged by relational integration in both abstract and action-related matrices. Data thereby extend previous findings beyond the abstract into the action domain, providing evidence for the domain generality of this network.

Furthermore, considering the contrasts between action and abstract matrices corroborated this finding: these contrasts did not reveal any significant activation differences in either aPFC or PMC, a result that could be confirmed by ROI analyses. Our first hypothesis, derived from traditional accounts of aPFC and PMC function, can thus be rejected: neither is PMC more involved than aPFC in relational processing in the action domain nor is aPFC more involved than PMC in relational processing in the abstract domain.

Considering the engagement of aPFC and PMC in relational processing guided by sequential and non-sequential rules, it was apparent that rule type also differentiated aPFC from PMC—but again, independent of domain. BOLD response in right ventrolateral PMC was significantly higher for sequential as compared to distributive rule problems, and this was true in both the action and the abstract conditions. In contrast, no area in aPFC responded to the rule type manipulation. For each sequential rule matrix, there existed a specific transformation command that could be applied to get from the first to the second stimulus in a row and again to get from the second to the third stimulus. Thus, adjacent entries within matrices could be readily concatenated into a coherent sequence by applying one transformation command. Stronger involvement of PMC under these conditions strengthens the argument for a role of this region in providing generic transformation styles for applications in different behavioral and cognitive domains (Schubotz, 2007). For instance, it has been shown that ventral PMC can be exploited for both action-related and abstract sequential representations (Schubotz and von Cramon, 2004). The present results inform this view in that they show that activation in PMC is not only elicited when sequential prediction is asked for, but also in a task in which stimuli are presented all at once but nevertheless related to one another by sequential relations.

Co-activations of PMC in this contrast were found in the anterior intraparietal sulcus (aIPS) and the motion sensitive area (MT), both of which are known to project to ventrolateral PMC (Ghosh and Gattera, 1995). The aIPS is known to provide ventrolateral PMC with pragmatically relevant object descriptions (Borra et al., 2008; Fagg and Arbib, 1998); area MT is engaged in the processing of motion (Grossman et al., 2000). These co-activations lend further support to the view that transformations in the cognitive-perceptual domain are to a certain extent comparable to those in the motor domain (Schubotz, 2007). Considering the present findings from this perspective, the notion of pragmatic relevance or pragmatic meaning can be more generally framed as pertaining to those properties of an object that are subjected to transformational computations in PMC. On the other side, activity in area MT suggests that by concatenation of matrix entries the imagination of dynamic transformation was elicited. This finding extends prior findings on area MT which has been suggested not only for the perception of motion, but also for the imagination of motion (Goebel et al., 1998) and for the perception of merely implied motion (Kourtzi and Kanwisher, 2000; Senior et al., 2000).

Our results relate to a growing literature on anterior prefrontal cortex and frontal organization in general. Specifically, the rostral part of the PFC has not only been implicated in relational integration in abstract matrices tasks but also in the integration of propositions for evaluating semantic analogies (Bunge et al., 2005; Green et al., 2006). We can now extend aPFC involvement in relational integration from the visuospatial and semantic domain to action-related cognition. Furthermore, this area has been shown to be central to functions such as branching and multitasking (Braver and Bongiolatti, 2002; Dreher

et al., 2008; Koechlin et al., 1999), leading to the development of several recent theories of anterior-to-posterior functional hierarchies within the PFC, some including the PMC (Badre, 2008; Badre and D'Esposito, 2007; Koechlin and Summerfield, 2007). One of these models proposes that action selection is guided by hierarchically ordered control signals, processed in a network of brain regions organized along the rostrocaudal axis of lateral PFC and premotor cortex (Koechlin et al., 2003). Thereby, rostral PFC is held to be central to behaviors and mental activities requiring simultaneous engagement in multiple tasks that are not serially organized into a pre-established superordinate plan, enabling it to overcome the serial constraints that are in effect in more posterior brain areas (Koechlin and Hyafil, 2007). Our finding that aPFC is activated for relational integration, whereas PMC is not, is supportive of these hierarchical models which postulate aPFC to become involved at the highest stages of executive processing. PMC's pronounced involvement in sequential rule matrices might, in addition, be indicative for this region's preference for serial cognitive processing, in accordance with the model of Koechlin and Hyafil (2007).

A further theoretical issue our data are relevant to is the ongoing question of process versus domain specificity in PFC organization. In domain-specific models, functional dissociations between brain regions reflect the same fundamental process operating on different categories of information, while in process-specific models, they reflect the operation of different processes, regardless of the type of information being processed (Gilbert et al., 2006). Our findings are particularly relevant to the notion that aPFC regions are domain-independent, whereas more posterior regions of the frontal lobes are domain-specific (Bunge et al., 2005; Sakai and Passingham, 2003; Smith and Jonides, 1999). Our study is a direct test of both a process-specific and a domain-specific hypothesis regarding two frontal areas, aPFC and PMC. Indeed, we could find no main effect of domain – abstract or action-related reasoning – in anterior prefrontal areas, in contrast to a region lying more posterior in prefrontal cortex. The ROI analysis confirmed that aPFC was engaged in relational integration in both domains. This result speaks in favor of domain-independent processing in aPFC. However, our data provided no evidence for selective involvement of PMC in relational processing in one of the two domains studied, either. Instead, PMC was preferentially activated for sequential processing, but again, in both domains. Consequently, our results are consistent with a domain-independent processing account of aPFC function but are inconsistent with a domain-specific account of PMC function. Our study therefore suggests that the dissociation of function between aPFC and PMC is process specific rather than domain specific.

Concluding remarks

With the present study, we aimed to make a contribution to clarifying the functional significance of two frontal brain areas, aPFC and PMC, in relational information processing. Our findings provide evidence that the respective roles of aPFC and PMC in relational processing are not primarily related to the abstractness of the relational information processed, i.e., to the informational domain. Rather, the functions of these areas seem to be differentiated by the type of relational processing, with lateral PMC being engaged for the concatenation of sequentially related entities into coherent sequences and aPFC for the integration of multiple relations in parallel.

Acknowledgments

We thank Andrea Gast-Sandmann and Heike Schmidt-Duderstedt for assistance in graphic layout and stimulus materials, Stefan Zysset and Jane Neumann for support in MRI methods and statistics, Bettina Johst for help in programming, and Bettina Gutsche for experimental assistance.

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