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Katrien Denys
K.U.Leuven Medical School

Wim Vanduffel
K.U.Leuven Medical School

Denis Fize
K.U.Leuven Medical School

Koen Nelissen
K.U.Leuven Medical School

Hiromasa Sawamura
K.U.Leuven Medical School

See next page for additional authors

Authors

Katrien Denys, Wim Vanduffel, Denis Fize, Koen Nelissen, Hiromasa Sawamura, Svetlana Georgieva, Rufin Vogels, David Van Essen, and Guy A. Orban

Visual Activation in Prefrontal Cortex is Stronger in Monkeys than in Humans

Katrien Denys[1], Wim Vanduffel[1,2], Denis Fize[1], Koen Nelissen[1], Hiromasa Sawamura[1], Svetlana Georgieva[1], Rufin Vogels[1], David Van Essen[3], and Guy A. Orban[1]

Abstract

■ The prefrontal cortex supports many cognitive abilities, which humans share to some degree with monkeys. The specialized functions of the prefrontal cortex depend both on the nature of its inputs from other brain regions and on distinctive aspects of local processing. We used functional MRI to compare prefrontal activity between monkey and human subjects when they viewed identical images of objects, either intact or scrambled. Visual object-related activation of the lateral prefrontal cortex was observed in both species, but was stronger in monkeys than in humans, both in magnitude (factors 2–3) and in spatial extent (fivefold or more as a percentage of prefrontal volume). This difference was observed for two different stimulus sets, at two field strengths, and over a range of tasks. These results suggest that there may be more volitional control over visual processing in humans than in monkeys. ■

INTRODUCTION

The primate prefrontal cortex is more developed compared with that of other mammals, and it plays a key role in some of the remarkable cognitive abilities of humans (Miller & Cohen, 2001; Roberts, Robbins, & Weiskrantz, 1998; Fuster, 1997; Passingham, 1993; Goldman-Rakic, 1987). Current hypotheses about the function of the prefrontal cortex emphasize both the importance of its connections with other brain regions and aspects of local processing involved in maintaining information on-line (Postle & D'Esposito, 1999; Goldman-Rakic, 1987) and/or response inhibition (Curtis & D'Esposito, 2003; Konishi et al., 1998; Dias, Robbins, & Roberts, 1996). Insights regarding the evolution of cognition may emerge from assessing the information reaching the prefrontal cortex in different primate species.

Recently, it has become possible to compare functional brain organization directly using fMRI in both humans and macaque monkeys (Tsao, Vanduffel, et al., 2003; Nakahara, Hayashi, Konishi, & Miyashita, 2002; Vanduffel, Fize, Peuskens, et al., 2002). Here, we investigated the responses of the prefrontal cortex to images of visual objects using stimuli known to activate the ventral visual association cortex of monkeys and humans (Denys et al., 2004; Tsao, Freiwald, Knutsen, Mandeville, & Tootell, 2003; Kourtzi & Kanwisher, 2000; Malach et al., 1995; Desimone, Albright, Gross, & Bruce, 1984; Gross, Rocha-Miranda, & Bender, 1972). This enabled us to compare the strength of visual signals reaching the prefrontal cortex in humans and monkeys. For this comparison, we scanned human and monkey subjects who fixated and viewed identical sets of visual stimuli, including familiar and novel drawings and gray scale images of objects as well as their scrambled counterparts (Figure 1).

RESULTS

Visual Activation in the Monkey Prefrontal Cortex

Monkeys' prefrontal cortex showed object-related activation, responding significantly more ($p < .05$ corrected for multiple comparisons over the whole brain; Friston et al., 1995) to intact than to scrambled images of objects. The object-related activation extended from the lower bank of the principal sulcus (PS) over the inferior frontal cortex (IFC) to the anterior bank of the inferior ramus of the arcuate sulcus (irAS) (Figure 2A). This latter activation is centered about 8–10 mm dorsal to the activation reported by Nakahara et al. (2002) in monkeys shifting cue (color or shape) in a modified Wisconsin Card Sorting Test. It was also located about 3–4 mm anterior and 2–3 mm lateral to the margin of the FEF, identified by its motion response (Vanduffel, Fize, Mandeville, et al., 2001). The prefrontal object-related activation was significant in both hemispheres of each of the four monkeys tested, with irAS and PS most consistently activated

[1]K.U. Leuven Medical School, Belgium, [2]MGH/MIT/HMS Athinoula A. Martino's Center for Biomedical Imaging, Charlestown, MA, [3]Washington University

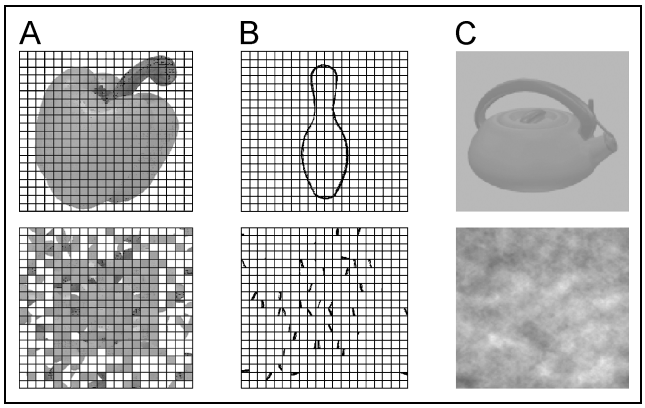

Figure 1. Stimuli: gray scale image (A) and drawing (B) of familiar objects (top) and their scrambled counterparts (bottom); stimulus set from Kourtzi and Kanwisher (2000). (C) Intact and phase scrambled images of simple man-made objects (courtesy of M. J. Tarr).

across hemispheres (Figure 2B). This frontal activation was symmetrical in the two hemispheres: on average ($n = 4$), 164 and 145 mm^3 were activated ($p < .05$, corrected) in the right and left hemispheres, respectively.

The magnitude of the scrambling effect can be appreciated from the activity profiles plotting the change in adjusted MR signal compared to the fixation control baseline in the local maximum of the activated region. The prefrontal responses (Figure 3A) were greater to intact images than to scrambled ones (main effect of scrambling) and more to gray scale images than to drawings (main effect of stimulus type). The interaction between these two factors was stronger in the PS than in the arcuate sulcus (AS). In line with this differential behavior of the PS and the AS, the effect of scrambling was stronger for familiar than for novel objects in the AS, but not in the PS. Finally, it is worth noting that all the MR responses to images were positive compared to the baseline fixation condition in the monkey.

The frontal activation was also observed (Figure 2C) when using different visual object and scrambled stimuli (Figure 1C) than in the original stimulus set (Figure 1A and B). Comparing small images of man-made objects to their phase scrambled counterparts, keeping the spatial frequency spectrum constant, yielded activation of the two same prefrontal regions in the two hemispheres.

Visual Activation in the Human Prefrontal Cortex: Main Experiment

In humans, a more restricted object-related prefrontal activation was observed. To increase sensitivity, a fixed effect model was applied to the 21 subjects tested in the main experiment. This analysis revealed only two small bilateral prefrontal activation sites at $p < .05$ corrected for multiple comparisons (Figure 4A). This contrasts with the monkeys in which many prefrontal voxels showed the effect of scrambling (Figure 4C). In order to estimate the extent of the cortical activation, we determined the total volume showing significant activation and expressed this as a percentage of the overall volume

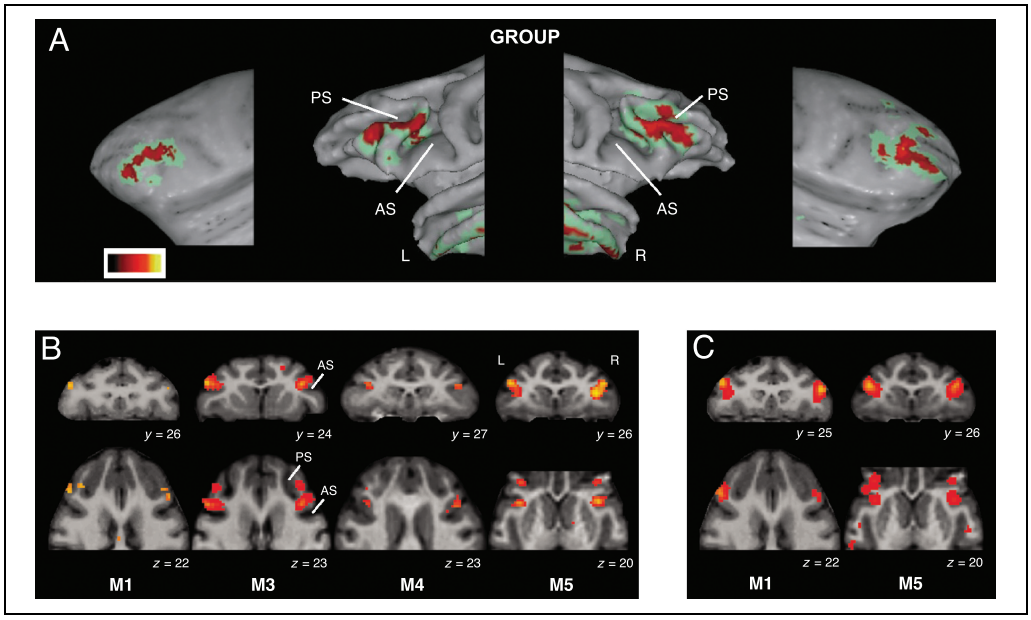

Figure 2. Shape sensitivity of monkey prefrontal cortex. (A) SPMs for the main effect of scrambling (group analysis of four monkeys, threshold at $p < .05$, corrected for multiple comparisons), projected onto the fiducial (middle pair) and inflated (lateral pair) configurations of the right and left hemispheres of M3. (B) SPMs for the main effect of scrambling ($p < .05$, corrected) projected onto coronal (top) and horizontal (bottom) sections of each of the four monkeys. (C) SPMs of the subtraction intact image of object minus phase scrambled image ($p < .05$, corrected) projected on coronal and horizontal sections of M1 and M5. In A–C, significant voxels are plotted in red to yellow color (see code in inset), maximum t-score was 13.1 in A, 12 in B, and 20.6 in C. In A, the neighboring pale green regions represent surface nodes lying within voxels that are not in themselves significant, but are immediately adjacent to significant voxels; this provides a reasonable approximation to the aggregate spatial uncertainties associated with the mapping process (coregistration of fMRI with structural MRI plus volume based registration from individual brains to the target M3 brain). In B and C, the y- and z-coordinates of the sections are indicated. AS = arcuate sulcus; PS = principal sulcus; R = right; L = left. Datasets are accessible for visualization or downloading via http://brainmap.wustl.edu:8081/sums/directory.do?dirid=1955018.

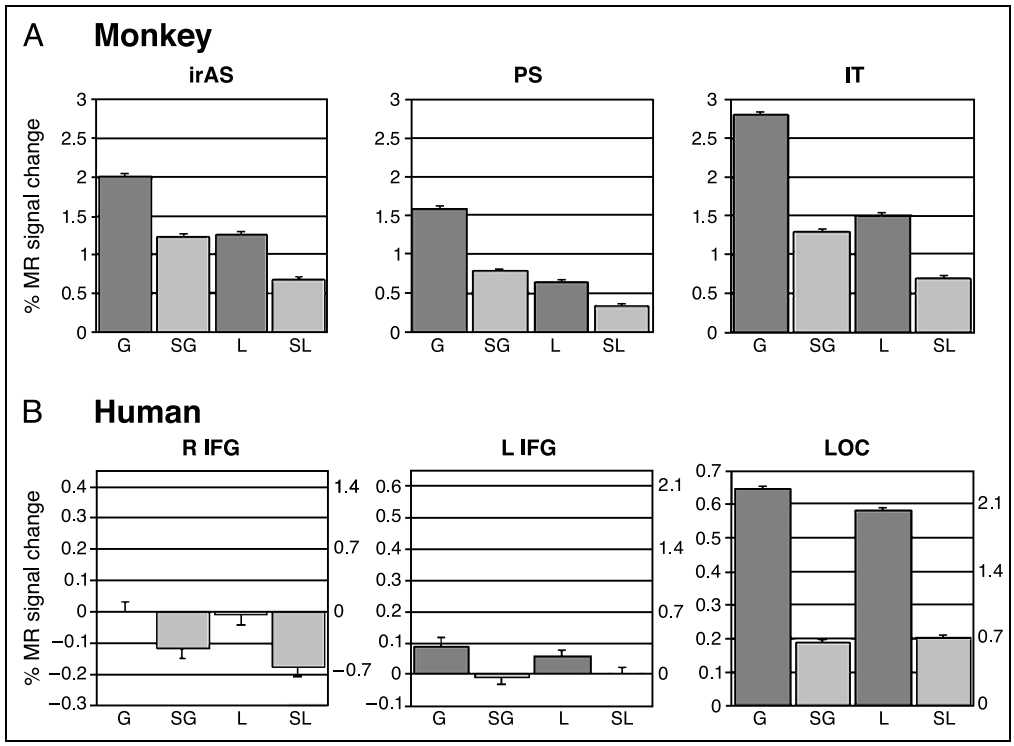

Figure 3. Activity profiles, plotting % MR signal change compared to fixation for the four experimental conditions, of monkey and human prefrontal regions (1.5 T data). (A) Profiles (n = 4) in the anterior bank of the irAS, in the lower bank of the PS and of the average of five local maxima in the inferotemporal complex. (B) Profiles (n = 21) in the right (48, 36, 12) and left (−42, 27, 18) human IFG (BA 45), corresponding to the local maximum of Site "2" in Figure 4A and of the average of five local maxima in the lateral occipital (LO) complex of both hemispheres. Vertical bars indicate SEMs. G = intact images gray scale objects; SG = scrambled counterparts; L = intact images of object drawings; SL = scrambled counterparts of drawings. In B the right-hand scale indicates the % signal change after correction for the lesser sensitivity of the BOLD compared to MION measurements: These values are more directly comparable to those in A. The profiles obtained with the BOLD HRF applied to the MION signals were very similar to those shown in A. For irAS, the % MR signal changes were 2.09, 1.34, 1.3, and 0.71 with the BOLD HRF applied to the MION data, compared to 2, 1.24, 1.3, and 0.67 with the MION HRF, that was used for the graph. For the PS the agreement was even closer (1.65, 0.9, 0.64, 0.34 for BOLD HRF and 1.58, 0.85, 0.62, and 0.31 for MION HRF).

in the prefrontal cortex (see Methods for details). For the macaque, the prefrontal object-related activation for the two hemispheres combined (447 mm^3) was 4.2% of the total volume of prefrontal cortex (10,620 mm^3). For the human, the prefrontal activation was only 0.9% of the prefrontal cortical volume (1593 mm^3 activation/ 177,000 mm^3), which is fivefold smaller than that of the macaque. One human prefrontal site ("1" in Figure 4A) was located in the middle frontal gyrus about 20 mm anterior to the lower part (pursuit related) of human FEF (Petit, Clark, Ingeholm, & Haxby, 1997) and posterior to the set-shifting activation of Nakahara et al. (2002). The other ("2" in Figure 4A) was located anterior to this set-shifting activation in the inferior frontal gyrus (IFG). Lowering the threshold to $p < .001$, uncorrected for multiple comparisons, did not reveal any additional prefrontal sites (Figure 4A; small patches on the lower right of the map are in the orbito-frontal cortex and are not considered significant in absence of a priori information). Again, the pattern and strength of activation was very similar in the two hemispheres: at $p < .001$, uncorrected level 3861 and 3824 mm^3 reached threshold in the right and left hemispheres, respectively. Figure 4D shows that neither prefrontal site corresponds to the location predicted by deforming the macaque to the human cortex using functionally corresponding landmarks (see Methods). Results were very similar for the scans in which images of familiar or novel objects were presented.

Control Analyses

Further lowering of the threshold to $p < .05$ uncorrected revealed no additional object-related foci in the human prefrontal cortex, indicating that false negatives are not a concern in the main experiment. Furthermore, we split the human subjects into five groups of four subjects, to match the number of monkey subjects. On each group, we performed a fixed effect analysis of the scrambling effect, exactly as was done in monkeys. There was no significant ($p < .05$, corrected) object-related prefrontal activation in three of these subgroups, and only a few voxels of Sites 1 and 2 were significant in the remaining two subgroups. Finally, at the single-subject level, only 6 of the 21 subjects showed a significant ($p < .05$, corrected, at least 5 voxels) prefrontal activation. Of these, three were experienced subjects (see Methods).

Control Experiments at 1.5 and 3 T

Six human subjects were tested with the small man-made object stimuli (Figure 1C) compared to their phase scrambled counterpart. Prefrontal object-related activation ($p < .001$, uncorrected) was largely restricted

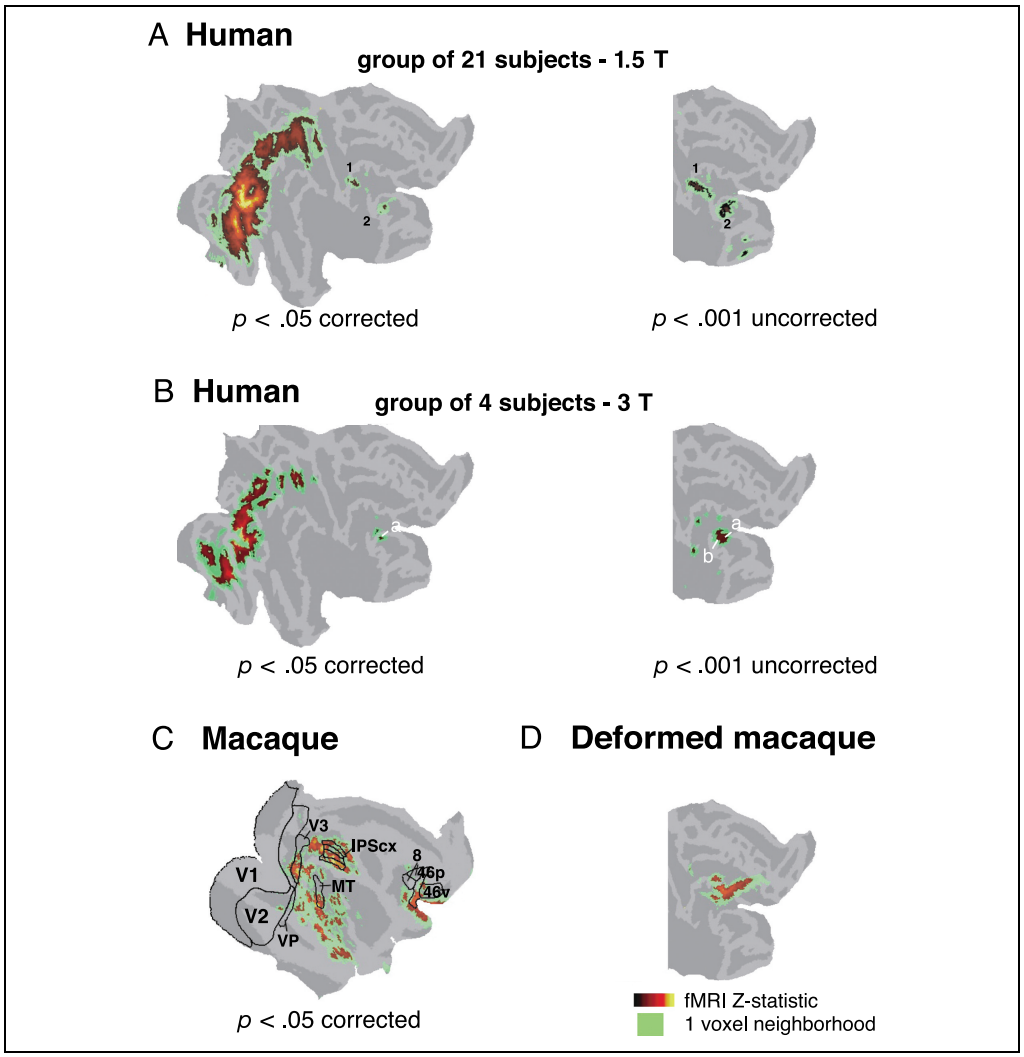

Figure 4. Flatmaps comparing human and monkey prefrontal activation. (A, left) SPM of the main effect of scrambling in human at 1.5 T (group $n = 21$, fixed effect, $p < .05$, corrected for multiple comparisons) on flattened right hemisphere of the human Colin atlas map (Caret software). (A, right) Activation in the right prefrontal cortex of humans at 1.5 T (group $n = 21$, fixed effect, main effect of scrambling, $p < .001$, uncorrected). (B, left) SPM of the main effect of scrambling in human at 3 T (group $n = 4$, fixed effect, $p < .05$, corrected for multiple comparisons) on flattened right hemisphere of the human Colin atlas map (Caret software). (B, right) Activation in the right prefrontal cortex of humans at 3 T (group $n = 4$, fixed effect, main effect of scrambling, $p < .001$, uncorrected). (C) SPM of the main effect of scrambling in monkey (group, fixed effect, $p < .05$, corrected for multiple comparisons) on flattened right hemisphere of the Macaque F99UA1 atlas map. (D) Predicted activation of the human prefrontal cortex obtained by warping monkey object-related activation for the right hemisphere (see Methods). 1: posterior MFG sites (BA 44/9), 2: IFG sites in BA 45/47; a and b voxels where the profiles shown in Figure 5A and B were taken. Same conventions as Figure 2A. Maximum *t*-scores are 43.7 in A (left), 6.1 in A (right; prefrontal cortex), and 17.7 in C. Black surface nodes indicate voxels reaching $p < .001$ uncorrected and pale green surface nodes correspond to voxels immediately adjacent to voxels reaching $p < .001$ uncorrected. (C) Boundaries of selected visual and prefrontal areas according to Lewis and Van Essen (2000) architectonics partitioning scheme are indicated. IPScx = intraparietal sulcus complex. Datasets are accessible for visualization or downloading via http://brainmap.wustl.edu:8081/sums/directory.do?dirid=702554.

to the right hemisphere in positions similar to those of Sites "1" and "2" of the main experiment (Figure 4A). The more anterior activation, in a position close to Site "2" of the main experiment (coordinates 56, 24, 30, compared to 48, 36, 12), occurred only in the right hemisphere (701 mm^3). Furthermore, this object-related activation was in fact a reflection of a stronger deactivation compared to fixation in the scrambled than in the intact conditions. Restricting the analysis in the main experiment to the more anterior Site "2" in fact yielded similar results: more object-related voxels in the right (1431 mm^3) than in the left (405 mm^3) hemisphere, with a scrambling effect in the right side that was mainly due to deactivation in the scrambling condition (Figure 3B).

Four human subjects were tested with the original Kourtzi and Kanwisher stimuli (Figure 1A and B) at 3 T. The main effect of scrambling again yielded a significant region (45, 30, 21) close to Site "2" of the main experiment (Figure 4B). Again there was an asymmetry in favor of the right hemisphere (1593 mm^3 compared to 54 mm^3 at $p < .001$, uncorrected) and again the right object-related activation was at least in part due to deactivation compared to fixation in the scrambling condition (Figure 5B), although in the local maximum of the right activation site most responses were positive compared to fixation (Figure 5A).

Asymmetry between Human Prefrontal Cortices

In the main and the two control experiments, a consistent object-related activation of the human prefrontal cortex near Site "2" was observed. In all three experi-

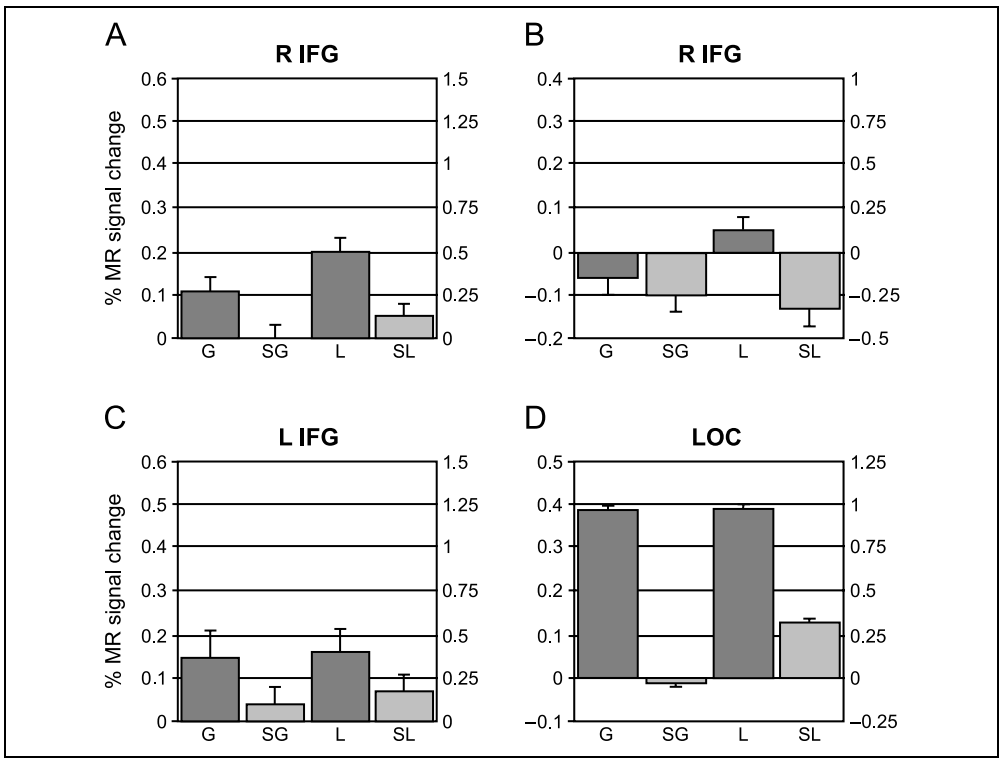

Figure 5. Activity profiles, plotting % MR signal change compared to fixation for the four experimental conditions (main experiment), of human prefrontal regions (3 T data). (A) Local maximum of the right IFG (45, 30, 21, A in Figure 4B), (B) other right IFG locus (51, 24, 27, B in Figure 4B), (C) local maximum of the left IFG (−51, 24, 30), (D) average of five local maxima of human LO. Same conventions as Figure 3.

ments, this activation was asymmetric, both in extent and in sign. In the right-sided foci, which were more extensive than the left ones, activity in the scrambled conditions was lower than in the fixation and intact images conditions (Figure 3B, Figure 5B). In the left-sided activation regions, on the other hand, MR activity in the intact conditions exceeded that in the fixation and scrambled conditions, as was the case for all monkey object-related foci (Figure 3B, Figure 5C). In order to evaluate separately the contribution of activation in the intact conditions and deactivation in the scrambled conditions, we compared the fixation minus scrambled-image conditions and the intact-image conditions minus fixation (Figure 6). This analysis showed in all three human experiments an extensive deactivation by the scrambled conditions (blue) mainly in the right hemisphere and little activation by the intact conditions (red). Thus, this analysis revealed that the asymmetry in object-related prefrontal activation, documented so far in the three human experiments, reflected an asymmetry in deactivation in the scrambled condition. This is very different from the monkey prefrontal cortex in which the scrambling effect was symmetric and mainly reflected activation by intact images compared to fixation (Figure 6B). Notice that other parts of the monkey prefrontal cortex were also deactivated, but again the pattern was symmetric (Figure 6B).

Because the monkey object-related activation was almost entirely due to activation in the intact conditions (Figure 3A and Figure 6B), we isolated this effect in the human prefrontal cortex by masking the regions showing a main effect of scrambling to include only regions with a positive activation for all stimuli averaged compared to fixation. This analysis selected for regions with a scrambling effect due to positive MR responses compared to fixation. In both the main experiment at 1.5 T and the 3 T study this yielded a small left-sided prefrontal activation, corresponding to the original object-related activation in that hemisphere (Figure 3B). No such activation was observed when using the small man-made object stimuli. The extent (at $p < .001$, uncorrected) of this positive activation was only 27 mm^3 in the 3 T study and 164 mm^3 in the main experiment. Applying a similar analysis to the monkey data yielded extents of 277 and 284 mm^3 in the right and left prefrontal cortex at $p < .001$ uncorrected. Thus, considering only positive, object-related activation yields an activation which represents only 0.05% of the human prefrontal cortex but 5% of the monkey prefrontal cortex, two orders of magnitude difference.

Comparison of Prefrontal Activation in the Two Species: Magnitude

Furthermore, the activity profiles of the left IFG (Figure 3B) in the main experiment and in the 3 T study (Figure 5C) show that the effect of scrambling is small in magnitude. In order to compare the monkey and human data, we compared the scrambling effect in the prefrontal cortex to that in the ventral cortex. The amplitude of the prefrontal scrambling effect was only about 20% of

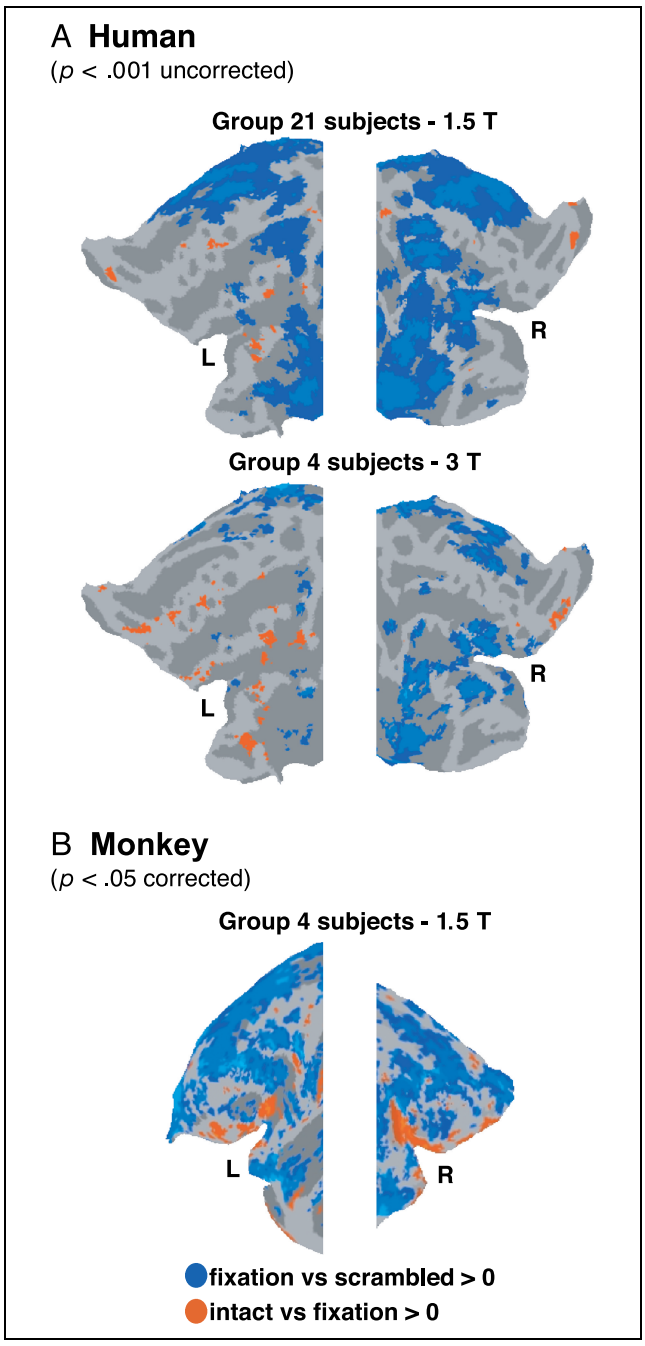

Figure 6. Flatmaps of human (A) and monkey (B) right (R) and left (L) prefrontal cortex showing voxels reaching $p < .001$ uncorrected in the subtractions fixation minus scrambled-image conditions (blue voxels) and intact-image conditions minus fixation (red voxels). In A both the 1.5 T data ($n = 21$) and the 3 T data ($n = 4$) are shown. Datasets are accessible for visualization or downloading via http://brainmap.wustl.edu:8081/sums/directory.do?dirid=702554.

that in the human lateral occipital (LO) complex in the occipital cortex in the main experiment (Figure 3B) and 25% in the 3 T experiment (Figure 5D). In contrast, the prefrontal activation in the monkey was about 60% of the activation strength in the inferotemporal complex (Figure 3A).

As an additional way to compare the amplitude of the prefrontal activation in human (BOLD signals) and monkey (monocrystalline iron oxide nanoparticle [MION] signals), we used the percent MR signal changes in V1 as a common reference. Both in Figure 3B and in Figure 5, the right-hand scale indicates the MR signal changes multiplied by a scale factor derived from the average V1 activation by the four stimulus conditions compared to fixation in order to compensate for the greater sensitivity of the contrast agent based MR scanning (Leite et al., 2002; Vanduffel, Fize, Mandeville, et al., 2001). Even with this correction of the percent MR signal changes (human BOLD data), the scrambling effect is clearly stronger in the monkey prefrontal cortex than in the human left IFG.

Finally, it could be argued that due to the slower time course of the MION hemodynamic response function (HRF) compared to the BOLD HRF (Vanduffel, Fize, Mandeville, et al., 2001), the difference in prefrontal activation between humans and monkeys may reflect a difference in time course of the prefrontal activity rather than in level. Therefore, we analyzed the monkey MION data with the BOLD HRF. The activity profiles of the monkey prefrontal cortex remained basically unchanged (see legend of Figure 3 for values), in agreement with our earlier study (Vanduffel, Fize, Mandeville, et al., 2001).

Thus, the prefrontal activation by object images in humans is small, both in extent and in magnitude. Whatever activation is present in humans is asymmetric in sign in the two hemispheres, only the left-sided activation reflecting positive responses to intact stimuli, as it does in monkeys.

Control Experiments for Attention

To control for possible differences in attention during passive viewing of intact and scrambled stimuli, we compared the effect of scrambling while two of the monkeys performed a high acuity task with a small central stimulus (Denys et al., 2004; Vanduffel, Fize, Peuskens, et al., 2002; Vanduffel, Fize, Mandeville, et al., 2001). The object-related prefrontal activation remained significant. Yet, the task itself produced a stronger activation of the PS site (Figure 7). Because this task only removes attention from the stimulus, we further tested one monkey with the two different dimming tasks, one drawing attention away from the stimuli, the other drawing attention to the stimulus. Again the object-related prefrontal activation was similar in the neutral condition (passive viewing) and the conditions in which spatial attention was manipulated (Figure 7). In this case, prefrontal activity in both the irAS and the PS increased with the tasks, as reported also in the parietal cortex (Denys et al., 2004).

In humans, attention had no consistent effect on the small left IFG object-related activation. The high acuity task tested in four subjects had little effect: The object-

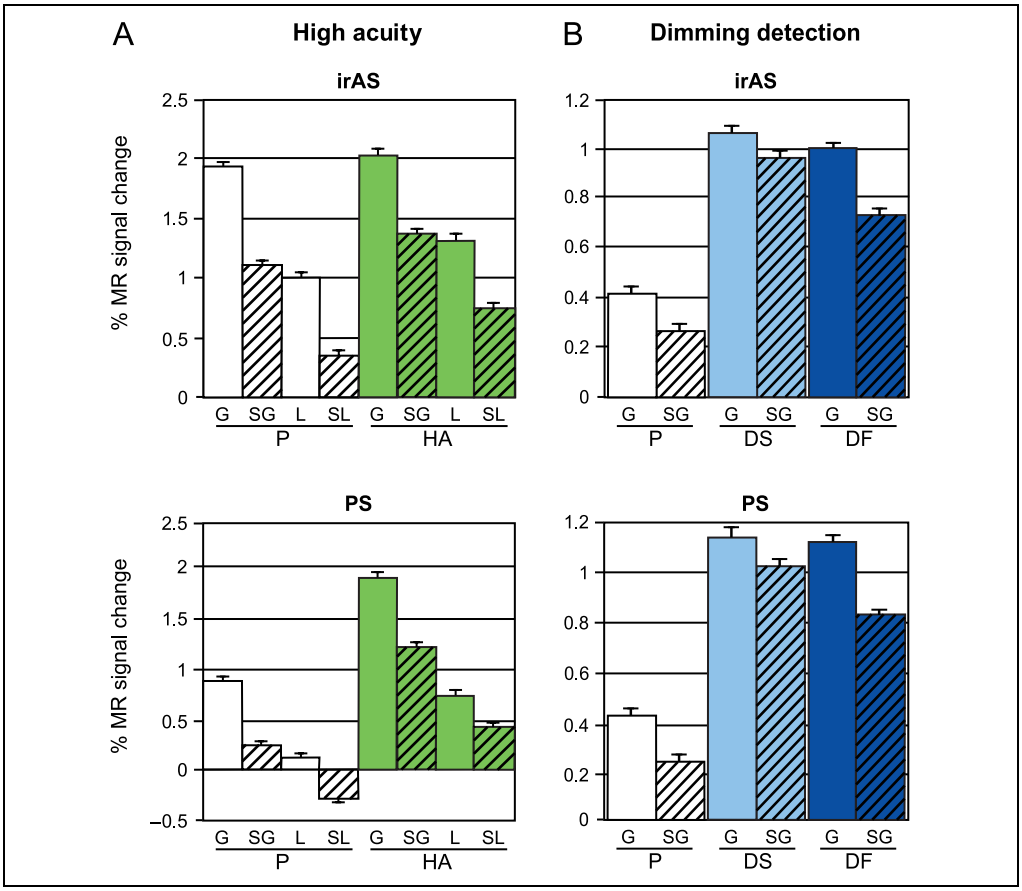

Figure 7. Activity profiles of the irAS and PS compared (M1 and M5) in passive (P) conditions and high acuity (HA) task (A) and compared (M3) in passive (P), dimming of stimulus (DS), and dimming of fixation point (DF) tasks (B). Hatched bars = scrambled conditions; open bars = intact images; white bars = passive; green = high acuity task; blue = dimming tasks.

related prefrontal activation in the left IFG remained unaltered. The dimming tasks, tested in three subjects with fewer time series administered per subject, reduced the object-related prefrontal activation. It should be noted that in both cases scrambling effects were fairly small in the passive condition: Only 21 voxels reached $p < .001$ uncorrected in the four subjects tested with high acuity and 11 voxels in the three subjects tested with the dimming tasks.

DISCUSSION

Our results in the monkey are in excellent agreement with many anatomical studies (Petrides & Pandya, 1999; Scalaidhe, Wilson, & Goldman-Rakic, 1997; Webster, Bachevalier, & Ungerleider, 1994; Ungerleider, Gaffan, & Pelak, 1989; Barbas, 1988; Petrides & Pandya, 1988) showing direct connections from V4 and the inferotemporal complex to the prefrontal cortex below the PS and in front of the irAS. In line with this, Scalaidhe et al. (1997) and Scalaidhe, Wilson, and Goldman-Rakic (1999) have called this IFC region the IT-recipient part of the prefrontal cortex. Consistent with this input from areas with a high proportion of shape-selective neurons, many single-cell studies have reported a high incidence of responses to complex visual shapes in macaque IFC (Asaad, Rainer, & Miller, 1998; Rainer, Asaad, & Miller, 1998; Scalaidhe et al., 1997). Scalaidhe et al. (1999) estimated the incidence of object-selective neurons to be smaller in the IFC than in IT. This is in accord with the relative magnitude of object-related activation in the inferotemporal versus the prefrontal cortex of the monkey observed in the present study (Figure 3A). The finding of Asaad, Rainer, and Miller, (2000) that many neurons near the PS are selective for the task demands fits with our observation that the task had a clear effect in this region, more so than in the AS. Finally, Tsao, Freiwald, et al. (2003) recently reported an object-related prefrontal activation using slightly different object and control stimuli.

The small magnitude and extent of object-related human prefrontal activation in the present study is consistent with the results from several other human imaging studies which used similar paradigms, included the prefrontal cortex in their analysis, and failed to observe a prefrontal activation by shape stimuli (Hasson, Levy, Behrmann, Hendler, & Malach, 2002; Levy, Hasson, Avidan, Hendler, & Malach, 2001). Furthermore, recent event-related fMRI studies that dissociate visual from working memory related components, have consistently reported prefrontal activation more related to the delay period than to visual stimulation (Druzgal

& D'Esposito, 2001; Rowe, Toni, Josephs, Frackowiak, & Passingham, 2000; Cohen, Perlstein, et al., 1997; Courtney, Ungerleider, Keil, & Haxby, 1997). In contrast, single-cell studies in the macaque using delay tasks have reported generally stronger visual responses compared to delay responses in the prefrontal cortex (Scalaidhe et al., 1999; Miller, Erickson, & Desimone, 1996; Wilson, Scalaidhe, & Goldman-Rakic, 1993; Fuster & Alexander, 1971). Further monkey fMRI studies are required, however, to exclude that fMRI is more sensitive to delay activity than single-cell recordings. The hemispheric difference observed in the human prefrontal cortex in the present study is consistent with other imaging studies showing that mainly the left prefrontal cortex is involved in semantic judgements of pictures (Vandenberghe, Price, Wise, Josephs, & Frackowiak, 1996) and in recall of specific pictures (Ranganath, Johnson, & D'Esposito, 2000).

Because the differences in human and monkey prefrontal activation by images of objects were observed over a range of attentional manipulations, it is unlikely that this simply reflects differences in attention to the stimuli. Similarly, differences in the way the tasks are performed by humans and monkeys seem unlikely as an explanation, as the central acuity task, and to a lesser degree, the dimming tasks, engage the subjects deeply. Using percent correct as an indication of the attentional load, the load was similar in the two species both for the high acuity and dimming tasks. Finally, the difference in visually driven activation between humans and monkeys is unlikely to depend on the novelty of the stimuli or on the experience with the scanning environment. Indeed, at least part of the human subjects were experienced as were the monkey subjects and results were very similar for familiar and novel stimuli in humans, as well as in monkeys, for which the distinction is less clear.

Several explanations, not mutually exclusive, can be advanced for the species difference in prefrontal function we observed. First, the type of information reaching the prefrontal cortex may be different, being more polysensory than visual in humans. This view is supported by our observation that object-related activation in the human occipito-temporal cortex (LO complex) does not extend nearly as far anteriorly in humans (terminating about 4 cm posterior to the temporal pole). In humans, anterior temporal regions are activated by nonvisual tasks, such as sentence understanding (Vandenberghe, Nobre, & Price, 2002). If the complete extent of human and monkey inferotemporal cortex projects equally to the prefrontal cortex, there will be relatively less visual input in the human compared to the monkey prefrontal cortex. Alternatively, there may be selective gating of the visual information reaching the prefrontal cortex (Cohen, Braver, & O'Reilly, 1996). By this hypothesis, the monkey prefrontal cortex would process visual information relatively automatically, whereas the human prefrontal cortex would have more volitional control over visual processing. At present, we can only speculate about the nature and the origin of such gating signals. The interhemispheric difference in prefrontal activity profiles (Figure 3B) is, however, consistent with a stronger gating of the object-related visual input in the right than in the left human prefrontal cortex. The gating is also consistent with the reports that the human prefrontal cortex is activated in semantic tasks involving pictures of objects (Vandenberghe, Price, et al., 1996) or in imagery of objects (Ishai, Ungerleider, & Haxby, 2000). Finally, the prefrontal cortex is proportionally larger in humans than in macaques (Semendeferi, Lu, Schenker, & Damasio, 2002), suggesting that new prefrontal areas or subareas may have emerged in humans. Thus, the object-related prefrontal activation might be equally large in relation to prefrontal cortical regions shared by humans and monkeys, but appear smaller in humans because of the new areas/subareas that emerged in humans. Also, these new areas might contribute to the putative gating signals.

The function of a cortical region depends on its inputs and on the local operations performed on these inputs. Indeed, interrupting IT input into the prefrontal cortex impairs the learning of stimulus–response associations (Bussey, Wise, & Murray, 2002; Eacott & Gaffan, 1992), which are key for the if–then tasks. These tasks are particularly vulnerable to prefrontal cortex lesions (Passingham, 1993). Hence, our finding that visual object-related activation is much stronger in the monkey than in the human prefrontal cortex may provide an important clue to the evolution of cognition. Indeed, a central postulate is that a controlling subsystem such as the prefrontal cortex learns the associations between cues, internal states, and actions that predict goal attainment or reward (Miller & Wallis, 2003). Such a mechanism determines which information is controlling behavior at any given time. Our results suggest that this selection itself is more under sensory control in monkeys than in humans. In that sense, our study complements the demonstration that similar prefrontal regions in the two species are engaged in set shifting (Nakahara et al., 2002). This latter study indicates that the prefrontal cortex in both species performs a similar local operation, while ours shows that the inputs on which the prefrontal cortex operates differ between the two species. Both studies illustrate the advantages of a comparative functional imaging approach, as the evolution of prefrontal cortex function can be assessed by powerful new tools that complement cytoarchitectonics and anatomical size comparisons (Semendeferi et al., 2002; Petrides & Pandya, 1999).

METHODS

Subjects

Four male (M1, M3, M4, and M5) rhesus monkeys (3–6 kg) and 24 young right-handed human subjects

were scanned in a 1.5-T (Siemens Sonata) scanner. (For surgical procedures, training of monkeys, details of image acquisition, and statistical analysis, see Denys et al., 2004; Fize et al., 2003; Vanduffel, Fize, Mandeville, et al., 2001). The monkeys were rewarded for fixating within a 2° × 2° window, while stimuli were projected in the background. Human subjects were instructed to maintain fixation and received a small monetary incentive after completion of all scan sessions. Eye position was monitored during scanning (using Iscan for monkeys and Ober2 for humans). Monkey subjects were sitting in a sphinx position in a plastic chair and faced the screen directly. Humans were lying on their back and viewed the screen through a 45° tilted mirror.

Before monkey scanning sessions, a contrast agent (MION) was injected intravenously (5–11 mg/kg). The use of the contrast agent improved the contrast-to-noise ratio (by a factor 5) and the localization to the gray matter compared to BOLD measurements (Leite et al., 2002; Vanduffel, Fize, Mandeville, et al., 2001). For the sake of clarity, the polarity of the MION MR changes, which are negative for increased blood volumes, were inverted.

All 4 monkeys and 21 human subjects participated in the main experiment at 1.5 T. This main experiment was replicated at 3 T in 4 of the 21 human subjects. Of the 21 human subjects tested at 1.5 T, 17 contributed data to the report of Denys et al. (2004). In the remaining four subjects, eye movements were not recorded to control for possible susceptibility artifacts on the prefrontal activation introduced by the monitoring device. Thirteen of the 21 subjects were experienced in the sense that they had already participated in at least two other scanning sessions, prior to the present scanning experiments. The remaining eight subjects were less experienced having participated in at most one session. Two of the four monkeys (M1 and M5) were scanned passively after they had been scanned with the high acuity task (see below) with the second stimulus set. Six human subjects were also scanned with this stimulus set at 1.5 T. Three of them, all experienced, had participated in the main experiment.

Stimuli and Tasks

Visual stimuli were projected from a Barco 6300 LCD projector (640–480 pixels, 60 Hz) onto a screen 54 cm in front of the monkeys' eyes (28 cm for humans). The stimuli of the main experiment were the very same stimuli as used by Kourtzi and Kanwisher (2000), projected at a size of 15° by 15° for monkeys (12° by 12° for humans). They included gray scale images (Figure 1A) and line drawings (Figure 1B) of objects and their scrambled counterparts. The stimuli were matched within the novel or the familiar sets, but not between sets. The second stimulus set consisted of images of man-made isolated objects (Figure 1C) on a gray background (courtesy of M. J. Tarr, Brown University, Providence, RI, http://titan.cog.brown.edu:16080/~tarr/stimuli.html) and phase scrambled images of these objects (size 7° by 7°). Stimulus presentation lasted 600 msec for both stimulus sets. A fixation point, 0.3° in size, was provided to both humans and monkeys. Neither the monkey nor the human subjects had seen the Kourtzi and Kanwisher stimuli prior to the scanning.

In the high acuity task, the subjects (4 humans plus monkeys, M1 and M5) had to detect the change in orientation of a very small bar (5 × 18 minarc) from vertical to horizontal, while the stimuli of the main experiment were presented just as in passive conditions. To respond, subjects interrupted an IR beam with one hand. In humans, the passive viewing and task runs alternated according to an ABBA design, whereas in monkey the task runs were administered after the passive viewing ones. Performance was similar in the two species (average 86% correct in humans and 79% in monkeys).

Three human subjects and one monkey (M3) performed two different dimming tasks. In the first task, the fixation point dimmed, while in the second a small part (on average 2° by 2.5°) of the stimulus dimmed. Dimming of a stimulus part could occur in any of 24 positions, within an eccentricity range of 1° to 5°. Intact and scrambled gray scale stimuli were presented as in the passive conditions and dimming occurred at random times for 200 msec. Timings of the dimming epochs were identical to those of the orientation changes in the high acuity task. In both dimming detection tasks, the amplitude of dimming was adjusted to control performance levels of the subjects. Performance of humans and monkeys in these tasks was similar ranging in both species between 84% and 89% correct in the different conditions of the two dimming tasks.

Scanning

Each functional scan consisted of gradient-echo echo-planar whole-brain images [TR=2.4 sec (3.01 sec for humans), TE = 27 msec (50 msec for humans), 64 by 64 matrix, 2 × 2 × 2 mm voxels (3 × 3 × 4.5 mm for humans), 32 sagittal slices]. For the scanning at 3 T (Philips), the parameters were set as follows: TR 3.3 msec, TE 30 msec, 64 by 64 matrix, 2.2 × 2.2 × 2.5 mm resolution, 46 horizontal slices. In the main experiment using the Kourtzi and Kanwisher stimuli, five conditions were tested: images of gray scale objects and their scrambled counterpart, drawings of objects and their scrambled counterpart and fixation baseline. In a typical block design (24-sec blocks), the presentation order of the five conditions within a run was randomized. In alternate runs images of familiar and novel objects were used. For the other stimuli (Figure 1C), three conditions were relevant for the present report: images of intact and phase scrambled objects and fixation only. In a separate session, an anatomical (3D-MPRAGE) volume (1 × 1 × 1 mm voxels) was acquired while the monkey was

anesthetized (for humans, a similar volume was obtained in one of the scan sessions).

Analysis

Data were analyzed using SPM99 (www.fil.ion.ucl.ac.uk/spm/), FreeSurfer (surfer.nmr.mgh.harvard.edu/), SureFit (brainmap.wustl.edu/SureFit/), and Caret (brainmap.wustl.edu/caret/). For the monkey experiments, only scans in which the monkey kept his fixation in the window 80% of the time were analyzed. In these experiments, realignment parameters, as well as eye movement traces, were included as covariates of no interest to remove movement artifacts (which was unnecessary in humans as movements were rare). The functional volumes were realigned and coregistered nonrigidly with their anatomical volumes using the Match software (Chefd'hotel, Hermosillo, & Faugeras, 2002). The functional volumes were then subsampled to 1 mm^3 and smoothed with an isotropic gaussian kernel (sigma 0.68 mm). The human functional volumes were realigned, rigidly matched to their anatomical volumes, normalized, subsampled to 27 mm^3 (for the group analysis, and to 8 mm^3 for single subjects) and smoothed with an isotropic gaussian kernel (sigma 3.4 mm for group analysis and 2.56 mm for single subjects). For each stimulus comparison significant MR signal changes were assessed using a map of *t*-scores (statistical parametric map, SPM) and using $p < .05$, corrected for multiple comparisons over the whole brain (Friston et al., 1995), as threshold (unless specified otherwise). In the main experiment, the four experimental conditions followed a factorial design with scrambling and type of image (or image cue) as factors. Main effects and interaction were assessed.

Activity profiles plotting MR signal change relative to fixation were obtained from the group analysis. Unless stated otherwise, they are calculated for a local maximum in the SPM by averaging the most significant voxel and six of his neighbors in both hemispheres. To attempt to equate the percent MR signal changes in the monkey and human scanning which used different signals (BOLD and MION), we sampled the activity in the four conditions of the main experiment compared to fixation in V1 of humans and monkeys. In the two species profiles were taken from 7 voxels at 1.5° eccentricity of dorsal and ventral V1 of the two hemispheres and averaged. As expected, the percent MR signal changes for MION in the monkeys exceed that of BOLD in humans by a factor 3.5 for the 1.5 T experiment and 2.5 for the 3 T measurements. Notice that these ratios are different from contrast-to-noise ratios, which we found to differ by a factor 5 at 1.5 T when comparing MION and BOLD within species (monkey) in our earlier study (Vanduffel, Fize, Mandeville, et al., 2001). This latter factor was an average taken over several cortical areas, including V1 for which the factor was larger than for other areas. Hence, the present correction factor for percent MR signal changes may be an overestimate.

The fMRI data from the four monkeys were registered to one of the individuals (M3) using a customized volume-based registration algorithm (Match) (Chefd'hotel et al., 2002). The algorithm computes a dense deformation field by composition of small displacements minimizing a local correlation criterion. Regularization of the deformation field is obtained by low-pass filtering. The data were then mapped to surface reconstructions of the M3 right and left hemispheres generated using SureFit (Van Essen, Lewis, et al., 2001). The surfaces run close to the mid-cortical thickness (layer 4) throughout each hemisphere. These surfaces and the associated fMRI data were registered to the macaque F99UA1 atlas (Van Essen, Harwell, Hanlon, & Dickson, in press; Van Essen, 2002; brainmap.wustl.edu:8081/sums) using surface-based registration of spherical maps, as constrained by sulcal landmarks on the individual and atlas hemispheres. The human fMRI data were mapped to the human Colin atlas (Van Essen, Harwell, et al., in press; Van Essen, 2002; brainmap.wustl.edu:8081/sums) surface in SPM-Talairach space, using a volume to surface mapping tool in Caret. The monkey and human atlas surfaces were registered to one another using surface-based registration and a set of landmarks for cortical areas that are highly likely to be homologous across species (Van Essen, Harwell, et al., in press; Denys et al., 2004; Orban et al., 2004). In the frontal cortex, these include the area 3/4 boundary along the fundus of the central sulcus, the posterior border of the frontal eye fields, the primary olfactory and gustatory cortex, and the fundus of orbital sulcus.

The volumes of significant activation were scaled in relation to the estimated volume of the prefrontal cortex in each species. In the macaque, the prefrontal cortex was specified as the cortex anterior to area 6 in the Lewis and Van Essen (2000) partitioning scheme; surface area was measured on the fiducial surfaces of the M3 (to which population data were mapped) right and left hemispheres (2520 mm^2 + 2790 mm^2, equal to 12.6% of the total cortical surface); cortical thickness was determined to be 2 mm on average based on measurements in the high-resolution MRI volumes of the macaque atlas brain. In the human, the prefrontal cortex was specified as the cortex anterior to Brodmann's area 6 as mapped onto the Colin atlas brain, except that it also included the frontal eye fields as delineated in fMRI studies, which includes part of area 6 as defined by Brodmann but not in more recent studies. The prefrontal surface area measured on the fiducial surfaces of the Colin atlas brain in the SPM99 version of Talairach space was 31,000 mm^2 and 28,000 mm^2 for the right and left hemispheres (27% of the total cortical surface). Average cortical thickness was determined to be 3 mm based on measurements of the high-resolution MRI volume of the

Colin atlas brain. We consider these estimates to be more reliable than ones based solely on surface area measurements, because additional spatial uncertainties arise when mapping the fMRI activations onto the cortical surface, and these can lead to either significant overestimates or underestimates of activated surface area according to the mapping parameters used.

In total, we obtained 6200 volumes in three sessions in M1, 18,760 volumes in six sessions in M3, 2400 volumes in two sessions in M4, 11,200 volumes in four sessions in M5, and 52,440 volumes in 24 humans. Datasets for on-line surface visualization (WebCaret) or downloading and off-line visualization (Caret) are accessible in SumsDB by hyperlinks indicated in Figures 2, 4, and 6.

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Reprint requests should be sent to Prof. Guy A. Orban, Laboratorium voor Neuro- en Psychofysiologie, K.U. Leuven Medical School, Campus Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium, or via e-mail: Guy.Orban@med.kuleuven.ac.be.

The data reported in this experiment have been deposited in the fMRI Data Center (http://www.fmridc.org). The accession number is 2-2004-116FQ.

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