Searching for a Salient Target Involves Frontal Regions

Claire Wardak1, Wim Vanduffel1,2,3 and Guy A. Orban1

1Laboratorium voor Neuro-en Psychofysiologie, K.U. Leuven Medical School, Campus Gasthuisberg, 3000 Leuven, Belgium, 2Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, MA 02129, USA and 3Department of Radiology, Harvard Medical School, Charlestown, MA 02129, USA

Wim Vanduffel and Guy A. Orban contributed equally.

Address correspondence to Wim Vanduffel. Email: wim@nmr.mgh.harvard.edu.

Searching for an object in a complex visual scene involves selection mechanisms. Generally, it is assumed that efficient “pop-out” search involves mainly bottom-up processing, whereas inefficient search requires pronounced top-down control over visual processing. We used functional magnetic resonance imaging in behaving monkeys to explore the functional network involved in efficient visual search. As a pop-out target automatically attracts spatial attention, we attempted to determine the regions involved in feature selection independently of the spatial allocation of attention. Therefore, monkeys were trained to perform a search task in which they had to covertly detect the presence of a salient target among distractor objects. Three tasks were used to control, as much as possible, for the spatial allocation of attention. These control tasks were matched with the task search for visual input and manual responses. Pop-out search, when compared with the control tasks, activated 3 frontal regions: frontal eye field, area 45, and a posterior portion of area 46, in addition to small activation sites in lateral intraparietal area and inferotemporal area TE. Our results show that efficient search involves frontal regions as much as visual regions and in particular that ventral prefrontal area 45 is involved in top-down control during efficient search.

Keywords: bottom-up, fMRI, monkey, top-down, visual search

Introduction

Given the large amount of visual information reaching the brain, it is critical that only the most pertinent information is retained for further processing and guidance of behavior. Visual attention is one mechanism that can select, at any moment, the most relevant information in spatial and/or featural terms (e.g., Posner 1980; O’Craven et al. 1999; Saenz et al. 2002). This selection can be based on the saliency of visual objects, such as a pop-out color or a sudden appearance, or on their behavioral relevance.

Visual search paradigms are well suited to study attentional selection mechanisms, particularly those of the feature selection process, because it is easy to manipulate visual properties of objects in the visual scene (Treisman and Gelade 1980; Wolfe et al. 1989). Such manipulations can render visual search efficient or inefficient. Traditionally it is assumed that efficient “pop-out” search involves mainly bottom-up processing, whereas inefficient search requires pronounced top-down control over visual processing (Treisman and Gelade 1980; Wolfe et al. 1989; Desimone and Duncan 1995; Corbetta and Shulman 2002). Alternative models, such as the guided search theory, suggest that attentional mechanisms participate in even the easiest searches (e.g., Joseph et al. 1997; Wolfe 1998; Horowitz et al. 2006). They propose that low-level visual areas by themselves cannot support efficient search and that either the involvement of high level cortical areas, where categorical information is available, is needed (reverse hierarchy theory, Hochstein and Ahissar 2002), or the participation of prefrontal cortex (PFC), which dynamically reconfigures the input filters in the visual areas (Di Lollo et al. 2001, 2005). Both efficient and inefficient searches involve several cognitive mechanisms including a spatial attention component (directing attention to the objects) and a feature-based selection component (identifying a target among distractors). These 2 mechanisms are often confused in efficient search in which the pop-out target exogenously attracts attention (Treisman and Gelade 1980; Wolfe et al. 1989).

In monkeys, several regions have been implicated in visual search: the dorsolateral PFC (Rainer et al. 1998; Buschman and Miller 2007), the frontal eye field (FEF; Schall and Hanes 1993; Thompson et al. 2005; Wardak et al. 2006); the lateral intraparietal area (LIP; Gottlieb et al. 1998; Bisley and Goldberg 2003; Wardak et al. 2004); and occipital visual areas, in particular area V4 (Ogawa and Komatsu 2004; Bichot et al. 2005). In these studies, however, it was difficult to disentangle the actual feature selection process from the spatial orientation of attention. Moreover, the different types of search paradigms and operant behaviors employed render between-study comparisons difficult.

In this study, we used functional magnetic resonance imaging (fMRI) in the awake monkey (Vanduffel et al. 2001) to determine the cortical network involved in detecting and selecting an oddball target defined by a single feature among visual distractors (i.e., pop-out search). We specifically aimed to identify 1) those regions activated during efficient target selection independently of spatial attention factors, and 2) which regions were involved in selecting the target while also being modulated by the spatial allocation of attention. Two monkeys were trained to manually signal the presence of a peripheral blue bar target among several red bar distractors. This is a typical efficient search or pop-out task in which the target is the oddball. In this task, the feature-based selection component includes at least 3 subcomponents: attention to the feature color, definition of the target as having a blue color, and detection of a target in the visual input. We designed 3 control tasks that allowed us to manipulate the spatial allocation of attention and to probe the functional network involved in target selection mechanisms. The aim of these controls was to gradually equalize the sustained components of spatial attention between search and control tasks. In these control tasks, the monkeys had to report a change in luminance of a restricted portion of the visual scene. This kind of task has been proven to be effective in orienting attention in the visual scene (Bushnell et al. 1981; Mountcastle et al. 1981; Kodaka et al. 1997). During the control tasks, spatial attention was either fixed in the central position, fixed in a peripheral location at the same eccentricity
as the search objects, or distributed across the same locations as those during visual search task. Comparing fMRI activity evoked during search and during the 3 control conditions allowed us to isolate the cortical regions involved in feature-based selection and to visualize the effects of spatial attention.

Materials and Methods

Subjects
Two male rhesus monkeys (M9 and M10, 3.5–4.5 kg, 4–5 years old) participated in the study. Animal care and experimental procedures met the national and European guidelines and were approved by the ethical committee of the K.U. Leuven medical school. The details of the surgical procedures, training of monkeys, image acquisition, eye monitoring, and statistical analysis of monkeys’ scans have been described previously (Vanduffel et al. 2001; Fize et al. 2003; Nelissen et al. 2005, 2006; Durand et al. 2007) and will be summarized only briefly.

Monkeys sat in a sphinx position in a plastic monkey chair positioned within the horizontal bore of the magnet (1.5-T MR scanner Sonata; Siemens, Erlangen, Germany), directly facing a translucent screen placed 56 cm from the eyes. The head was restrained by means of an MR-compatible plastic headset implanted on the skull and a radial receive-only surface coil (10-cm diameter) was positioned above the head. Eye positions were monitored at 50 Hz during scanning using a pupill-corneal reflection tracking system (RK-726PCI, Iscan, Cambridge, MA). During the task, monkeys could produce a manual response by interrupting an infrared light beam to receive a liquid reward.

Tasks
The monkeys were trained on a visual search task and 3 tasks used to control for the sustained allocation of attention. The details of the stimuli, tasks, timing of events, and training procedures are described in the supplementary methods (see also Fig. S1). The main elements are summarized below.

In the visual search task, the monkeys had to detect the presence of a blue bar target presented among 1, 3, or 7 red distractors that were physically identical to the target except for their color (Fig. 1A). In half the trials, 2, 4, or 8 red distractors without target were presented. All items were presented along a circular path at 7° eccentricity. In order to be rewarded, the monkeys had to indicate with a manual response whether the pop-out target was present. In all tasks, the monkeys maintained fixation during stimulus presentation and responded manually. The control tasks were very similar to the search task, except that the monkeys had to maintain their attention either centrally, or at a fixed, or at a random peripheral location (Fig. 1A). During the central control task, the monkeys were rewarded for reporting the brightening of the fixation point. In the fixed peripheral control task the monkeys had to report the brightening of a fixed peripheral portion of the background that occurred at the same eccentricity as the target and distractors items. This brightening event occurred in only 1 of the 4 quadrants. During the random peripheral control (rpc) task, the monkeys also had to report the brightening of a portion of the peripheral background, but in this task, the brightening occurred randomly in all 4 quadrants. A brightening event occurred randomly in only 50% of the trials of the 3 control tasks, and the target appeared in 50% of the search trials. In addition to being rewarded for correct responses, the monkeys were also rewarded for withholding their response on trials without a brightening event or target.

During the fMRI scans, the search task was mixed with one of the 3 control tasks and a fixation-only condition. When averaged over the duration of an epoch, the presentation of blue and red bars and brightening events was exactly matched between the search and the respective control condition. Some control trials contained only blue bar stimuli, and half the search trials contained a brightening at the end (see Fig. S1A). Obviously, the monkeys had to ignore the brightening events that occurred at the end of the search trials. Only the color of the fixation point, which indicated the nature of the task, differed between tasks.

Scanning
Before each scanning session, a contrast agent, monocrystalline iron oxide nanoparticle (MION) or an equivalent compound with a different trade name (Sinerrim), was injected into the animal’s femoral/saphenous vein (+11 mg/kg). Compared with blood oxygenation level-dependent measurements, this improved the contrast-to-noise ratio by a factor of 5 as well as the spatial sensitivity (Mandeville and Marota 1999; Vanduffel et al. 2001; Zhao et al. 2006). For the sake of clarity, the polarity of the MION MR signal changes, which are negative for increased blood volumes, was inverted.

We acquired gradient-echo echoplanar images covering the whole brain (1.5 T; repetition time 2.4 s; echo time [TE] 27 ms; 32 sagittal slices with a 64 × 64 matrix; 2 × 2 × 2-mm voxels). Data were acquired using a block design. Each functional time series or “run” consisted of 4 repetitions of 3 conditions (Fig. S1C)—fixation baseline (10 functional volumes/epoch), visual search (15 functional volumes/epoch), and control task (15 functional volumes/epoch)—for a total of 160 functional
volumes or 384 s. Two presentation orders were used wherein the fixation condition always came first, followed by either the visual search or the control condition. This order was kept constant within a given run.

We obtained 3 independent data sets for visual search, each slightly different, depending on the type of control condition used during the acquisition. Within a given run, the visual search and a given control condition were always tested with the same number of objects (2, 4, or 8). Together with the 2 orders of presentation, this yielded a total of 18 different runs. During each scanning session, the runs with different orders, different numbers of items, and different control conditions were pseudorandomly intermixed. On average, 16 runs (range 7–13 runs) were tested daily depending on the degree of cooperation shown by the monkey. When all 18 possible run orders were not tested on a given day, the remaining runs were tested on the following day.

From both monkeys, we acquired data for the visual search mixed with the central control and for visual search mixed with the fixed peripheral control conditions during the first scanning period. After a period of rest (2 weeks), both monkeys were trained on the rpc condition. In a second scanning period, data for the visual search mixed with the rpc task were acquired. During a third scanning period, we performed 3 localizer experiments: standard retinotopic mapping, single bar mapping, and eccentricity mapping (see Supplementary methods for details). In total, 55 960 functional volumes were acquired in M9 and 551 80 volumes in M10.

**Analysis**

The runs were selected for analysis on the basis of the monkey’s behavior (quality of fixation >85% and similar performance in the visual search and control tasks). In the final selection of data, the number of trials, hence the number of visual presentations, did not differ significantly between the 2 behavioral conditions (visual search and one of the 3 controls). The number of target/brightening presentations for each of the 4 spatial quadrants was also matched.

Time series were analyzed using an adapted version of SPM99 (Friston et al. 1999; Wellcome Department of Cognitive Neurology, London, United Kingdom) and MATCH software. For spatial preprocessing, functional volumes were first realigned and rigidly coregistered with a high spatial resolution (0.35 × 0.35 × 0.35-mm voxels acquired at 3 T at the Martins Center for Biomedical Imaging, MA, United States) template anatomy (M12, or MM1 in Ekstrom et al. 2008) in stereotactic space. The MATCH algorithm (Chef’d’Hotel et al. 2002; Hermosillo et al. 2002) then performed a nonrigid coregistration (warping) of a mean functional image onto the template anatomy (see Supplementary methods). Fixed effect group analyses were performed with an adjusted number of volumes per monkey (including the same number of trials from each monkey) and with the same number of volumes for the 2-, 4-, and 8-item conditions. The variability between monkeys was small and 8-item conditions. The variability between monkeys was small.

**Behavior**

Both monkeys performed well during the functional data acquisition. The 60 best runs of each data set, based on performance during the visual search and control tasks and on fixation quality, were included in the group analyses. These groups of 60 runs included equal numbers of 2-, 4-, and 8-item runs. In the visual search conditions, the slope of the reaction time as a function of the number of items (Fig. 2A) ranged from −3.52 ms/item (vs/cc, \( P = 0.007 \)) to +0.70 ms/item (vs/rpc, \( P > 0.5 \)) in M10, and from −0.45 ms/item (vs/rpc, \( P > 0.5 \)) to +0.18 ms/item (vs/fpc, \( P > 0.8 \)) for vs/cc, \( P > 0.9 \)) in M10, which is consistent with the definition of efficient (pop-out) visual search.

Both task difficulty and fixation accuracy were matched between visual search and control tasks in the 60 runs selected. The percentage correct trials did not differ (\( P > 0.15 \)) between the 2 tasks, in each data set and each monkey (Fig. 2B). For the 3 data sets and the 2 monkeys, we tested for differences in percentage fixation within a 1.5° × 2° window, the number of saccades per minute, and the standard deviation of the eye position in the x and y dimensions. None of these tests showed significant differences (\( P > 0.05 \) for all the tests), except for the standard deviation of the eye position in the x dimension for the vs/cc data set in M9 (Fig. 2C and D). The total number of motor responses was similar in all tasks (chi-square \( P > 0.4 \)).

**General Network Involved in All Tasks: Search and Control Tasks versus Fixation**

We first determined the cortical areas involved in the search and control tasks compared with fixation baseline. We performed a conjunction analysis of the 2 contrasts comparing visual search and the control task of each data set with fixation. This allowed us to determine the common network involved in all 4 tasks. The analysis revealed a large bilateral network composed of visual (V1, V2, V3, V3A, V4, MT, FST, TEO, TE, and TEa), parietal (LIP), and frontal areas (F2, F5, FEF, 45B, 45A, 46, surrounding the local maximum coordinates, excluding any voxels outside the gray matter or outside the targeted bank of the sulcus. Statistics performed on the MR signal changes were analysis of variances (ANOVs) supplemented by Bonferroni correction for multiple comparisons as post hoc analyses.

In addition to the voxel-based analyses, we also performed region of interest (ROI) analyses. The definition of the ROIs and their use, as well as the cortical flattening procedures, are detailed in the Supplementary methods.

**Results**

Surrounds: In addition to the voxel-based analyses, we also performed region of interest (ROI) analyses. The definition of the ROIs and their use, as well as the cortical flattening procedures, are detailed in the Supplementary methods.

**General Network Involved in All Tasks: Search and Control Tasks versus Fixation**

We first determined the cortical areas involved in the search and control tasks compared with fixation baseline. We performed a conjunction analysis of the 2 contrasts comparing visual search and the control task of each data set with fixation. This allowed us to determine the common network involved in all 4 tasks. The analysis revealed a large bilateral network composed of visual (V1, V2, V3, V3A, V4, MT, FST, TEO, TE, and TEa), parietal (LIP), and frontal areas (F2, F5, FEF, 45B, 45A, 46v,
Figure 2. Behavioral results obtained in the scanner, restricted to the sessions used in the group analyses. The shades of red (inset) correspond to the visual search conditions, the shades of blue correspond to the control conditions, the difference in luminance/saturation indicating the control condition with which it was mixed (see inset). (A) Mean reaction time (ms ± standard error of the mean [SEM]) for the various task conditions plotted as a function of the number of objects. (B) Performance (% correct trials) for the different task conditions. No significant difference was observed between the 2 tasks paired in a given time series. (C) Mean percentage of fixation and the mean number of saccades per minute as a function of task condition. No significant difference was observed between the 2 tasks paired in a given time series. (D) Mean standard deviation of the eye position in the X and Y dimensions as a function of task condition. *P < 0.05, 1-way ANOVA, no significant difference in any of the other comparisons.

Figure 3. General network activated by the visual search and the control conditions. (A) Statistical parametric maps (SPMs) of conjunction analysis (group of 2 monkeys) of 3 contrasts, comparing visual search and a control task of a given data set with fixation, P < 0.001 uncorrected for each individual contrast, displayed on the fiducial representations of the 2-folded hemispheres using Caret (Van Essen et al., 2001; http://brainmap.wustl.edu/caret). Sulci: arc: arcuate sulcus, ce: central sulcus, ios: inferior occipital sulcus, ips: intraparietal sulcus, ls: lateral sulcus, lu: lunate sulcus, ps: principal sulcus, and sts: superior temporal sulcus. (B) Same results as in A but displayed on flattened representations of the 2 hemispheres. Note that differential activation in the general network was observed in ventral V1-4 at a lower threshold (P < 0.005 uncorrected in each subtraction).
and orbitofrontal cortex) as illustrated in Figure 3 (see also Table S1). Medial frontal and anterior parietal areas, as well as the superior frontal gyrus and anterior cingulate cortex (ACC), were predominantly activated in the left hemisphere. In addition, the common network for the 4 tasks included left unilateral activation sites covering parts of the medial bank of the intraparietal sulcus (IPS [PE]), and somatosensory (areas 1, 2, SII), motor (F1/3), and premotor areas (pre-SMA/F6), contralateral to the right hand, which was used to respond. These unilateral regions were activated equally during the 4 different tasks. In Figure S2, the individual contrasts are displayed for search and each control condition versus fixation only. These data confirm that a large bilateral network of areas, as described above, is activated during both visual search and the individual control conditions. This also indicates that both functional networks largely overlap.

**Visual Search Compared with the 3 Control Tasks**

We compared the visual search condition with each of the 3 control conditions (see yellow color code in Fig. 4). We observed activations in frontal, parietal, and occipital visual areas. The “visual search versus central control” contrast revealed a major bilateral frontal activation (covering FEF, parts of areas 45 and 46), a bilateral orbitofrontal activation,
Specific visual search network. SPMs of conjunction analysis (Fig. 5). This network is composed of a bilateral frontal site (FEF/45/46), a bilateral parietal site (LIP), and some very restricted unilateral activations (TE, M1/S1, and superior arcuate). The individual monkey analyses showed activations in the same regions plus some additional small visual, parietal, and cingulate activations (Figs. S3 and S4).

The "visual search versus fixed peripheral control" contrast revealed the most restricted network of the 3 comparisons (Fig. 4). This network is composed of a bilateral frontal site (FEF/45/46), a bilateral parietal site (LIP), and some very restricted unilateral activations (TE, M1/S1, and superior arcuate). The individual monkey analyses showed activations in the same regions plus some additional small visual, parietal, and cingulate activations (Figs. S3 and S4).

The "visual search versus rpc" contrast revealed bilateral frontal activations (FEF/45/46), a bilateral parietal activation (LIP), and bilateral and unilateral visual activations (V1, V2, V3, V4, MT, and TE). The individual monkey analyses (Figs. S3 and S4), revealed the same network, yet a little more widespread in visual cortex (both monkeys) and in the frontal and parietal cortices (M9).

Control versus Search Task

We also compared each of the 3 control conditions with its respective visual search condition (Fig. 4 blue-colored regions). This analysis showed higher activity during the control task mainly in near-central representations of early visual areas and TEO (i.e., representations of the area between the fixation point and the location of the bars). We also observed bilateral activations in ventral premotor cortex, corresponding to area F5 (see Fig. S5 for the activity profiles of area F5). Some F5 neurons have visuomotor properties (e.g., Murata et al. 1997; Joly et al. 2009) that may be involved in the apparent "deactivation" during search.

The deactivation results in early visual cortex can be expected for the central control versus search contrast, as during the control condition the monkey had to attend to the central fixation point. In addition, it has been shown that attending to peripheral locations creates a deactivation in central visual regions (Tootell et al. 1998). Our results show a foveal deactivation for search relative to the control condition, although both tasks contain a spatial attention component.

Specific Network Involved in Visual Search

In order to isolate the core network involved in efficient visual search, we conducted a conjunction analysis between the 3 contrasts subtracting one of the control tasks from its respective visual search task. The goal of this analysis is to reveal the intersection of the 3 individual networks presented in Figure 4, revealing those regions that are significantly activated in each of the 3 individual contrasts vs/cc, vs/fpc, and vs/rpc. This analysis revealed a restricted network (Fig. 5) composed of 2 bilateral frontal activation sites in the arcuate sulcus and on the ventral convexity between the arcuate and principal sulci (covering parts of FEF, area 45 and area 46), one restricted bilateral activation in the lateral bank of the IPS (area LIP), and a unilateral site in right inferotemporal cortex (area TE). These activations were observed in both the group and individual monkey analyses (Table S2). Because this restricted set of search-specific sites are revealed by all 3 subtractions (vs/cc, vs/fpc, and vs/rpc), we will focus on these regions in the remainder of the Results section.

Frontal Regions

Contrary to our expectations, the search-specific activations are more widespread and stronger in prefrontal compared with occipital cortex (see Figs. 4 and 5, Figs. S3 and S4). Therefore, we performed a more detailed analysis on prefrontal areas in and surrounding the arcuate and principal sulci (Fig. 6). The search-specific activation in FEF was restricted to the part neighboring area 45B, consistent with the representation of the bar objects within this area, as assessed by the eccentricity localizer test (Fig. 7). A second search-specific frontal activation was observed in ventrolateral PFC, overlapping area 45A and neighboring area 46v (Fig. 6A,B).

ROI analyses (see Supplementary methods for ROI definitions) were performed in FEF, areas 45A, 46v and also area 45B, located between FEF and 45A. In these 4 regions, the visual search and each of the 3 control tasks elicited a significant MR signal change relative to the fixation baseline (Fig. S6). In some

Figure 5. Specific visual search network. SPMs of conjunction analysis (p = 2) of 3 contrasts, visual search versus each control task |P| < 0.001 uncorrected for each individual contrast, masked to display only positive signal change relative to the fixation baseline) are displayed on the flattened representations of both hemispheres using Caret. The black outlines represent the contours of the general network presented in Figure 3. The white arrow indicates the right TE activation site. See Figure 3 for abbreviations.
of the ROIs, the activation level during search, relative to fixation, differs among the 3 types of runs. This is to be expected because there were small differences between visual stimuli used in the search conditions because they were adapted to the respective control condition.

**FEF Is Functionally Different from Areas 45A, 45B, and 46v**

We observed distinct activity profiles when comparing search with each of the 3 control conditions (Fig. 6C). The activity profile of the FEF is significantly different from the profile in the other ROIs (3-way interaction of the ANOVA task × type of control × region: \( P < 0.0001 \) for the comparison FEF/46v, \( P < 0.0001 \) for FEF/45A and \( P = 0.0026 \) for FEF/45B). The FEF activation for search remained roughly constant relative to the various control conditions. This profile suggests that FEF is engaged not only in attention-related processes but also in a process specific to the visual search condition yet independent of the spatial allocation of attention, most likely reflecting target-feature selection processing (Fig. 1B).

In 45A, we observed a large difference between activations in the search and the central control condition and less so between search and the 2 peripheral control tasks. A similar activity profile was observed in area 45B, but only the difference between search and the central condition was significant. The latter effect explains the lack of significance for area 45B in the conjunction analysis between search and the 3 control conditions (Fig. 5). In area 46v, we obtained a similar profile, except that no difference between the search and the rpc was observed.

We assessed the reproducibility of these profiles by performing a ROI analysis on the subgroups obtained by separately
analyzing odd and even runs included in the 3 group analyses (Fig. S7). Two-way ANOVAs (task subgroup) were performed for each of the 3 experimental conditions (vs/cc, vs/fpc, and vs/rpc) and for each ROI. No significant interaction was observed except in 1 of 12 cases (vs/rpc in 45A), indicating that the results of the ROI analysis are reproducible.

Area 46v Is Functionally Different from Areas 45A and 45B
Our results revealed that an efficient visual search task activates several prefrontal cortical areas. The previous analyses revealed no major functional differences between area 46v and 45A and 45B. However, as detailed in the Supplementary information and Figure S8, we observed task-switching-related activity in areas 45A and 45B irrespective of the nature of the switches. Such switching-related activity was significantly different in area 46v, which only showed such activity for switches between visual search and the central control conditions. Hence, this additional analysis points to different functional roles of areas 45A and 45B on the one hand and area 46v on the other hand.

Parietal Regions
Visual search specifically activated one region in the lateral bank of the intraparietal sulcus. Using the independent localizer scans (see Supplementary methods), this region could be identified as LIP (Fig. 8A; Durand et al., 2007). The activity profile at the LIP local maximum (Fig. 8B) was very similar to that of FEF, even when we analyzed the FEF signal at the local maximum instead of the ROI. In both areas, the difference between search and control conditions was independent of the type of control condition. We also tested the reproducibility of the LIP profile by assessing the MR signal at the local maximum defined in the search-specific conjunction analysis for each of the 6 subgroups defined earlier (Fig. S7). No significant interaction was observed in the 2-way ANOVAs tested (task × subgroup for vs/cc, vs/fpc, and vs/rpc), indicating that the results of the analysis are reproducible.

It is noteworthy that the LIP activation specific to search was rather restricted when compared with the extent of LIP as defined by the localizers and to the portion of the LIP activated by all the tasks (general network, Fig. 3). The search-specific activation was observed in the middle of the LIP, whereas the anterior part of the LIP was activated equally well by the search and the 3 control tasks in both hemispheres (Fig. 8C). This observation also fits recent fMRI data suggesting that area LIP is not functionally homogeneous (Durand et al. 2007).

Visual Regions
Visual regions were well activated in our experiment as illustrated in Figure 3 (see also Table S1). Their activation was sensitive to the number of items presented (see Supplementary information). However, most visual regions were equally well activated by visual search and the 3 control tasks (Fig. S2). When compared with each of the control conditions separately, efficient visual search elicited the most

Figure 7. Visual search and FEF. (A) Eccentricity localizer in M10 in FEF, displayed on the left arcuate sulcus flat map. The blue area delimits the region in the anterior bank of the arcuate sulcus where the “small” eccentricity ring (covering 2.7°–5.3°) elicits more activation than the “middle” eccentricity ring (5.5°–8.5°), the “large” eccentricity ring (9°–13°) and the central 0.2° (color-changing fixation point). The green area delimits the region where the middle eccentricity ring elicits more activation than the other conditions. The localizer of the individual bars of the visual search activated a very similar region in the FEF. The pink area delimits the region where the large eccentricity ring elicits more activation than the other conditions. Most of this representation is in agreement with microstimulation data (e.g., Bruce and Goldberg 1985), the small saccade neurons being found in the most lateral part of the FEF and the large saccade neurons in the most medial part. However, our data also show a representation of large saccades at the FEF border near the fundus of the arcuate sulcus. This representation may be located in another area representing large saccades, alternatively FEF may effectively represent large saccades in this region overlooked by most electrophysiological experiments because it is difficult to reach. (B) SPM of the conjunction analysis (n = 2) of the 3 contrasts (each at P < 0.001 uncorrected) visual search versus each control condition, displayed on the left arcuate sulcus flat map (same results and same conventions as in Fig. 6).
visual activations when compared with the central control (Fig. 4, Figs. S3 and S4). Nearly no visual region was activated when the search was compared with the fixed peripheral control (at $P < 0.05$, corrected level, Fig. 4), whereas the visual activations were more extended when the search was compared with the rpc (although this was more variable across individuals, compare M9 and M10 results in Figs. S3 and S4). As a result, no specific activations remained when we compared the visual search to all 3 control conditions in the main conjunction analysis (Fig. 5, Table S2), except for the site in right TE (Fig. 5 white arrow). A left activation in TE was observed at a lower threshold. The activation profile at TE’s local maximum mirrored the profile of area 45: We observed a greater difference between search and the central control than between search and either of the 2 peripheral controls (Fig. 9). The reproducibility of this TE activation was tested as for the other areas (Fig. S7). No significant interaction was observed in the two-way ANOVAs task × subgroup for vs/cc, vs/fpc, and vs/rpc.

In the visual search versus central control contrast, the most significant local maximum was located in area V4 (Figs. 4 and 10.4), known to be involved in visual search (e.g., Bichot et al., 2005). This local maximum reached significance in the group and each of the subjects and was contained within the V4 region defined by the bar localizer test (Fig. 10.4 green outlines, Fig. 10C). The activation profile of this local maximum shows that the difference between search and the central control was no longer present when we compared search with either of the 2 peripheral controls (Fig. 10B).

**Discussion**

A large network of areas was activated by the 4 tasks used in our experiment (Fig. 3, Fig. S2, and Table S1). Most of these areas were equally well activated by both the search and control tasks, and they most likely participate in mechanisms common to all tasks like, for instance, visual processing, motor planning, motor response, and reward evaluation. A functional
network of mainly frontal regions, but also including parietal and occipital regions, was specifically involved in efficient visual search, irrespective of the type of control condition (Figs. 4 and 5, Figs. S3 and S4). Among these regions, FEF and LIP showed an activation level that was also independent of spatial attentional factors (as tested by the different control conditions in which the locus of spatial attention was varied). On the other hand, areas 45, 46v, and TE showed search-specific activations that were modulated by spatial attention.

This network of areas was common to both monkeys. Some small functional differences between the 2 monkeys were observed, especially in visual cortex. These functional differences may be explained by the small differences in reaction times observed between the 2 animals (Fig. 2A).

Figure 10. Visual search and early visual regions. (A) SPMs of the contrast visual search versus central control \( P < 0.001 \) at uncorrected level, masked to display only positive signal changes relative to baseline, \( n = 2 \) displayed on the posterior part of the flattened representations of both hemispheres using Caret. Same conventions as in Figure 4. (B) Profiles at the V4 local maximum. The histograms display the differences in MR signal (percent signal change ± SEM) between the visual search and each of the 3 controls in the 2 hemispheres (vs/cc: visual search compared with central control; vs/fpc: fixed peripheral control; vs/rpc: rpc). \(* P < 0.05, ** P < 0.001 \) for a t-test. (C) SPMs of 2 examples of individual bar localizers displayed on coronal sections of the brain. For each location, we contrasted the presentation of the bar at that location with the presentation of the bar at any location situated in another quadrant (masked to display only positive signal changes relative to baseline, \( n = 2 \)).
Our results showed only a few visual areas that were more active in search compared with all 3 control conditions. Frontal involvement in efficient visual search was not entirely unexpected as we know that neurons in FEF can signal the presence of a target presented among distractors (e.g., Schall and Hanes 1993). Yet, the prevalence of prefrontal over occipital visual activations was unpredicted by the traditional view of efficient search as a low-level preattentive task (Treisman and Gelade 1980; Desimone and Duncan 1995). Our results are thus in favor of more recent theories suggesting that high level cortical areas are crucially involved in efficient search, including higher order visual areas (Hochstein and Ahissar 2002), attention-related areas (Wolfe 1998; Horowitz et al. 2006) and frontal regions (Di Lollo et al. 2001, 2005).

The FEF–LIP Attentional Network

In our task, FEF and LIP were specifically involved in visual search and exhibit the same activity profile (Figs. 6C and 8D): The signal difference in these 2 areas between the search and the controls did not depend on the nature of the control condition. Because the controls differed in spatial allocation of attention, the FEF and LIP activations in our experiment cannot depend on spatial attention alone, but must also reflect a task component specific to visual search, most likely the feature selection process. The involvement of FEF and LIP in target selection has been shown in many single-cell studies (e.g., Schall and Hanes 1993; Bichot and Schall 2002; Sato et al. 2003; Ipata et al. 2006, 2009). One of the mechanisms involved in this selection is the specific representation of the relevant objects, or potential targets, in the visual scene. An explicit representation of the potential target is particularly needed when it is in direct competition with other objects sharing the same shape, the same eccentric location, and the same presentation onset as the target. The search-specific activations in FEF and LIP could represent the saliency of the target among competing distractors, in agreement with studies suggesting that these areas house a saliency map of the visual scene (Gottlieb et al. 1998; Thompson and Bichot 2005), or the locus of visual attention (Ipata et al. 2006; Serences and Yantis 2007). The purpose of a saliency map is to enhance the representation of behaviorally relevant locations/objects among competing objects. Indeed, deficits following reversible inactivation of LIP or FEF are observed in search tasks, only when the target is presented in competition with at least one object (Wardak et al. 2004, 2006). It is important to emphasize that in our task, the target–distractor competition is much stronger during search compared with control trials, because the distractors are similar to the target in shape, orientation, and location, and appear at the same time during the search but not during the control tasks.

It has been proposed that FEF and LIP contribute to spatial shifts of attention (Robinson et al. 1995; Moore and Fallah 2001). Therefore, it is surprising that the activation profiles in FEF and LIP are similar for all 3 control conditions. In our search and control tasks, however, spatial attention is most likely maintained at one location (or at a fixed eccentricity), thereby making our tasks unsuitable for making inferences about shifts of attention.

Only a few human fMRI studies on efficient search have shown an activation within the IPS (Leonards et al. 2000; Geng et al. 2006; Anderson et al. 2007) and the FEF (Anderson et al. 2007), pointing in particular to the role of the IPS in selection mechanisms (Geng et al. 2006). Contrary to the present monkey study, no regions in ventrolateral or inferior frontal cortex were activated, with the exception of the right ventrolateral PFC, which is commonly activated by efficient and inefficient search compared with a fixation baseline (Nobre et al. 2003).

Involvement of Ventrolateral PFC in Pop-Out Search

Efficient search activated 2 regions within the ventrolateral PFC, areas 46v and 45. Although search-specific activation levels in both areas depended on the spatial allocation of attention, the functional roles of areas 46v and 45 are significantly different, as shown by the analysis of switch events between tasks.

Area 46v

Area 46v exhibited a graded activation profile, showing greater differences between the search and the control condition as differences in allocation of spatial attention in the 2 conditions increased. When this allocation was similar, as in the rpc and visual search, no difference in MR signal was observed. These observations indicate that area 46v may play a role in the maintenance of spatial attention (Lebedev et al. 2004). The switch-associated profile of area 46v (Fig. S8) is compatible with this functional role, because significant switch-related activation is observed only for switches between visual search and the central control (or vice versa), when attention has to be redeployed from the periphery to the center (or vice versa).

Area 45

Area 45 exhibits a statistically different activity profile compared with area 46v. Activity during search differed significantly from activity during all 3 controls, but the difference was largest between search and the central control. Thus, area 45 participates in the selection process, and distinguishes between sustained central and peripheral attention. Moreover, the observation that area 45 is activated during the switch between tasks—a moment at which expectancies, rules, and targets change—suggests that this region exerts a top-down influence during search.

Neurons in ventrolateral PFC respond to both spatial and featural visual information (Rao et al. 1997). A recent fMRI study in humans showed that the inferior frontal junction, which may correspond to ventrolateral PFC in monkeys, can represent spatial and featural foreknowledge of an upcoming target in a visual search task (Egner et al. 2008). This area could thus code the target in featural and spatial terms. Neurons in this region have been shown to code a no-go alternative when this alternative was color-based (but not motion-direction based, Sakagami et al. 2001). This result suggests that area 45 might essentially represent "what not to respond to," thereby indirectly defining the target. Alternatively, area 45 might be activated by differences in motor inhibition between the search and the control conditions (Aron et al. 2004). During search, the monkey had to ignore a peripheral luminance change at the end of the trial.

In humans and monkeys, area 45 is also activated during set switching in a Wisconsin task, when the rule defining what to look for is changed (Nakahara et al. 2002), or during the updating of a rule in a working-memory task (Montojo and Courtney 2008). The switching activation in area 45 could be...
explained either by an inhibition of the previous task set (Nakahara et al. 2002) or by a resetting of "what to look for." Lesions of the ventrolateral PFC (including area 45) in the monkey, and a parallel fMRI study in humans, have shown a crucial role of this region in the switching of top-down attentional control on the basis of task demands (Rossi et al. 2007, 2009). These possible functional roles for area 45—target coding, rule definition, and task switching—are in line with the proposal that human inferior frontal cortex is involved in the selection and maintenance of task sets (Koechlin et al. 2003). Considering these possible interpretations, a functional involvement of area 45 would not be restricted to visual search but to a wide variety of cognitive tasks.

Area 45 is an ideal candidate for exerting a top-down influence on other portions of the search network, as it is anatomically connected to the FEF, LIP, and TE (Petrides and Pandya 2001). Furthermore, it is also connected to area 46v (Rempel-Clower and Barbas 2000), which could orient sustained attention signals toward the center or the periphery of the visual field, in order to inform visual areas like TE (Rempel-Clower and Barbas 2000) where to expect the target.

**Dorsolateral PFC**

Most studies on PFC in primates have concentrated on the dorsolateral PFC, mainly area 46 (of which area 46v, as we defined it, is only a very small ventrolateral part). Single-cell studies have shown that neurons in dorsolateral PFC can maintain spatial information during a delay (Funahashi et al. 1989), signal behaviorally relevant stimuli (Rainer et al. 1998), and differentiate the target from the distractor objects in visual search (Hasegawa et al. 2000; Iba and Sawaguchi 2002; Everling et al. 2002, 2006). Considering its proposed role in target selection, the lack of dorsolateral PFC activity in our experiment, even in the general network (Fig. 3), is rather surprising. One possible explanation for this result is that in all these studies a localized response (saccade) had to be made to a localized target. In our experiment, the monkey was required to make a nonlocalized hand response when the target was present, whatever its position. This interpretation is consistent with human fMRI studies of visual search. Visual search fails to activate the human equivalent area, especially in efficient search tasks (Leonards et al. 2000; Anderson et al. 2007). However, human area 46v is activated when a subject has to select one location in working memory and produce an appropriate localized hand response, suggesting a role of this region in attentional selection, or attention to the selection of action (Rowe and Passingham 2001; Lau et al. 2004).

**Activations in Visual Areas**

One visual region, TE, was consistently activated in the visual search task when contrasted with each of the 3 control conditions. This activation was very small (Fig. 5), probably reflecting some variability in its location between the 2 monkeys (Figs. S3 and S4). Physiological, behavioral, and imaging data (Komatsu et al. 1992; Heywood et al. 1995; Tootell et al. 2004) indicate that TE participates in color processing. Its activation in our task is thus consistent with a color-defined target and a modulation by featural attention, perhaps reflecting feedback from area 45. Moreover, TE (Fig. 9) showed a modulation of activity by the spatial allocation of attention (central vs. peripheral). TE is directly connected to area 46v (Rempel-Clower and Barbas 2000), which is involved in the voluntary allocation of spatial attention (Lebedev et al. 2004). TE may be activated because visual search involves higher order visual areas (Hochstein and Ahissar 2002). Alternatively, TE was specifically activated because we used a color-defined target during pop out. This implies that other visual areas would have been activated if the target was defined by a feature other than color (e.g., area MT for motion pop out).

The signals recorded in fMRI and electrophysiology are fundamentally different (Logothetis et al. 2001). In addition, fMRI relies on subtraction. Hence, we cannot completely rule out the possibility that the visual areas were activated similarly by search mechanisms during the visual search condition and by other cognitive mechanisms during the control condition, resulting in a null subtraction. The lack of search-specific activation in early visual areas in our experiment may also be explained by several stimulus or task-related factors, none of which challenge the involvement of visual regions in efficient search suggested by single-cell studies. First, the target was present only in 1 of 2 trials, and it was presented in competition with other bars that could have triggered the antagonistic surround of a number of visual neurons (Moran and Desimone 1985). Second, most of the early visual areas show significant activation when compared with the central control condition (Fig. 10A, Fig. S3 and S4). Visual activations in the search versus rpc (vs/rpc) contrast were robust but variable between subjects. Reliable and consistent visual activations were observed only in the search versus central control contrast (vs/cc). In this contrast, the activation at the local maximum in V4 showed a significant difference between search and the central control. The 2 other controls, in which spatial attention was allocated peripherally, as in the search, elicit as much signal in these regions as the visual search (Fig. 10B)."
Funding
Human Frontiers Science Program (HFSPO), GSKE, IUAP 6/29, EF/05/014, FWO G151.04, and G.0.622.08, NSF grant BCS-0745436, and Fyssen Foundation (C.W.).

Notes
The authors are indebted to A. Coeman, C. Fransen, M. Depaep, W. Depuydt, P. Kayenbergh, G. Meulemens, and A. Molcard for help with the experiments. They also thank G. Luppino for helping in defining the anatomical regions of interests and A. Roberts, J.D. Schall, R. Vogels, R. Vandenberge, J.-R. Duhamel, and S. Raiguel for invaluable comments on earlier versions of the manuscript. The laboratoire Guerbet (Roissy, France) provided the contrast agent Sinerem. Conflict of Interest: None declared.

References


