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Automatized clustering and functional geometry of human parietofrontal networks for language, space, and number

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Human functional MRI studies frequently reveal the joint activation of parietal and of lateral and mesial frontal areas during various cognitive tasks. To analyze the geometrical organization of those networks, we used an automatized clustering algorithm that parcels out sets of areas based on their similar profile of task-related activations or deactivations. This algorithm allowed us to reanalyze published fMRI data (Simon, O., Mangin, J.F., Cohen, L., Le Bihan, D., Dehaene, S., 2002. Topographical layout of hand, eye, calculation, and language-related areas in the human parietal lobe. Neuron 33, 475–487) and to reproduce the previously observed geometrical organization of activations for saccades, attention, grasping, pointing, calculation, and language processing in the parietal lobe. Further, we show that this organization extends to lateral and mesial prefrontal regions. Relative to the parietal lobe, the prefrontal functional geometry is characterized by a partially symmetrical anteroposterior ordering of activations, a decreased representation of effector-specific tasks, and a greater emphasis on higher cognitive functions of attention, higher-order spatial representation, calculation, and language. Anatomically, our results in humans are closely homologous to the known connectivity of parietal and frontal regions in the macaque monkey.

Keywords: Parietofrontal network; Language; Calculation; Visuospatial; fMRI; Automatic clusterization

Introduction

Functional magnetic resonance imaging has become an invaluable tool to analyze the anatomical organization of functional areas in the human brain. The organization of human visual areas, in particular, has seen considerable progress thanks both to the existence of previous work in animals (Van Essen et al., 2001) and to the presence of retinotopy as a major organization factor (Hasson et al., 2003). The major principles of geometrical organization of the parietal and frontal lobes, however, have proven more elusive (see, however, Astafiev et al., 2003; Buccino et al., 2001; Culham and Kanwisher, 2001; Koechlin et al., 2003). The parietal cortex currently appears as a mosaic of distinct specialized areas involved in a variety of visuospatial tasks including finger pointing, grasping, and eye or attention orienting (Simon et al., 2002). Likewise, the human frontal lobes are implied in a variety of cognitive processes such as motor programming, working memory, memory retrieval, executive control process, attentional selection, conflict resolution, and decision making, whose neural substrates are only beginning to be delineated. Furthermore, parietal and frontal activations often overlap in a variety of tasks, either because those regions are organized in a much less rigid fashion than posterior sensory-motor areas (Dehaene et al., 1998; Duncan and Owen, 2000), or because the tasks often share abstract components such as attention orienting or working memory. Interestingly, frontoparietal networks have also been found in resting state conditions where the level of attention load is measured with EEG (Laufs et al., 2003).

As a first step toward clarifying the anatomical organization of the parietal lobe, in a previous fMRI study, we scanned the same subjects during the performance of four visuospatial tasks (grasping, pointing, saccades, and visuospatial attention) and two cognitive tasks (calculation and phonemic detection) (Simon et al., 2002). Those tasks were selected because they were known to involve the parietal lobe. We observed a systematic anterior-to-posterior organization of activations in the parietal lobe, with subregions associated with grasping only, grasping and pointing, all visuomotor tasks, attention and saccades, and saccades only. We also demonstrated that the higher cognitive tasks of calculation and

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language lead to distinct activations of the inferior parietal lobule, within the intraparietal sulcus, that occupied reproducible geometrical locations relative to the above sensorimotor map. This overall organization was comparable to the known anatomy of macaque monkey areas and suggested putative human homologs of the monkey areas AIP, MIP, V6A, and LIP.

The aim of the present study is to extend those results by further characterizing, using fMRI during the same six tasks, the functional organization of the human frontal lobe and the geometry of parietofrontal networks. In our previous study, we acquired scans covering the whole of the parietal and frontal regions (though not the lower temporal and occipital lobes). However, our analysis was voluntarily limited to a mask covering the parietal lobe. This was done in part for practical reasons, as we had to manually explore the 31 possible intersections of active areas in each of our six tasks ($2^6 - 1$). The restriction to the parietal lobe also allowed us to limit the risk of false positives related to the large number of possible task intersections that we analyzed.

To extend this initial analysis to both parietal and frontal networks, we used a clustering method, adapted to functional images by three of us (F.K., G.F., and J.B.P.), that permits the automatized detection of sets of areas with a common profile of functional activation. The main idea is that regions or voxels can be described most adequately by its response profile across a range of different task. Our method thus uses the similarity of functional response profiles measured in distant brain regions to provide an automated classification of voxels into "classes" forming putative brain-scale networks. The *K*-means clustering algorithm that we use is one of the simplest and most popular classification techniques, and its description can be found in many textbooks. Thus, our main objective is not to describe this method, but rather to demonstrate how it allows extension of our previous results to the frontal lobe, thus yielding a better description of functional parietofrontal networks. Related ideas have been pursued in a few recent papers (Bokde et al., 2001; Passingham et al., 2002; Shinomoto et al., 2002), but practical examples are still rare.

In a nutshell, our method starts from the six three-dimensional images that characterize activations in each of the six tasks of interest. Each cerebral voxel is therefore characterized by a profile of six statistical values (Student's *t* tests), each of which defines the significance of activation in a given task relative to its control. Limiting the analysis only to voxels active in at least one task, the method groups together voxels that exhibit a similar profile of activation across the six tasks. The grouping is done regardless of whether the voxels are close or distant in cortical space. In the end, the voxels end up being grouped into functionally homogeneous sets of area (technically called "classes" in this paper), each of which is characterized by a maximally homogenous response to different tasks. Crucially, the analysis proceeds without ever specifying which profiles of activation are expected. Thus, the method is able to discover areas specifically activated by a single task, just as easily as areas activated by the intersection of several tasks.

Application of this method to our previous data set allowed us to isolate eight different functional networks, most of which have a parietal, a lateral frontal, and a mesial component. We demonstrate that the parietal components tightly reproduce our earlier findings with a manual method. The availability of the frontal components of these networks allows us to better understand the pathways linking the frontal and parietal lobes, their global geometry, and their possible relation to macaque monkey circuits.

Methods

Stimuli and tasks

Examples of the stimuli and tasks are presented in Fig. 1. Details have been published elsewhere (Simon et al., 2002). Briefly, cerebral activation was studied in six conditions: saccades, pointing, visuospatial attention, grasping, phoneme detection, and subtraction.

- In the saccade task, subjects moved their eyes toward a filled white square that appeared at random locations on a peripheral circle; the control task was central fixation.
- The pointing task was similar except that the subject pointed their right index finger at the peripheral target, while maintaining their gaze on the central box; again, the control was pointing continuously to the central location.
- In the attention shifting task, subjects detected random flashes of a filled white square that appeared at predictable locations on a peripheral circle. This task induced covert shifting of attention to the most probable location of the upcoming item (see Corbetta et al., 1998). The control was detection of similar flashes at the central location.
- In the grasping task, stimuli were eight different outline shapes appearing in 10 different orientations and in four different colors (green, blue, red, or yellow). Subjects shaped and oriented their right hand, mimicking the gesture that would be appropriate in order to grasp each object. The control was naming the color of the object.
- In the phoneme detection task, stimuli were French concrete words, 5–8 letters long, and subjects had to mentally sound out the word on the screen and to press a right-hand button if the word contained the sound "e" or "ε". The control involved viewing a random string of consonants and pressing the key if it consisted of uppercase letters.
- In the calculation task, stimuli were Arabic digits from 2 to 9. Subjects had to subtract each number from a fixed reference (11 in the first run, 15 in the second) and to mentally name the result. The control was mental naming of uppercase letters.

Image acquisition and analysis

Functional MR images were acquired on a General Electric Signa 1.5-T whole-body scanner. Sequence parameters were Gradient-echo EPI, TE = 60 ms, TR = 2 s, flip angle = 90°, slice thickness = 3.8 mm, interslice gap = 0, image matrix = 64 × 64, FOV = 192 × 256 mm, functional voxel size = 3.75 × 3.75 × 3.8 mm^3. Eighteen axial slices were acquired covering the parietal lobe and the majority of the prefrontal cortex, excluding orbitofrontal, lower temporal, and occipital cortices. Each task sequence consisted of ninety-seven 18-slice scans, the first four of which were not analyzed. Three-dimensional high-resolution anatomical images were also acquired (TE = 2.2 ms, TR = 10 ms, flip angle = 10°, inversion time (TI) = 600 ms, matrix = 256 × 192 mm, FOV = 220 × 165 mm, 128 sagittal slices, slice thickness = 1.5 or 1.2 mm).

The data from each individual subject were processed with Statistical Parametric Mapping software (SPM99). After motion correction, we normalized data to the Montreal Neurological Institute (MNI) template and applied a minimal spatial smoothing (5 mm). We then performed a group analysis using a random-

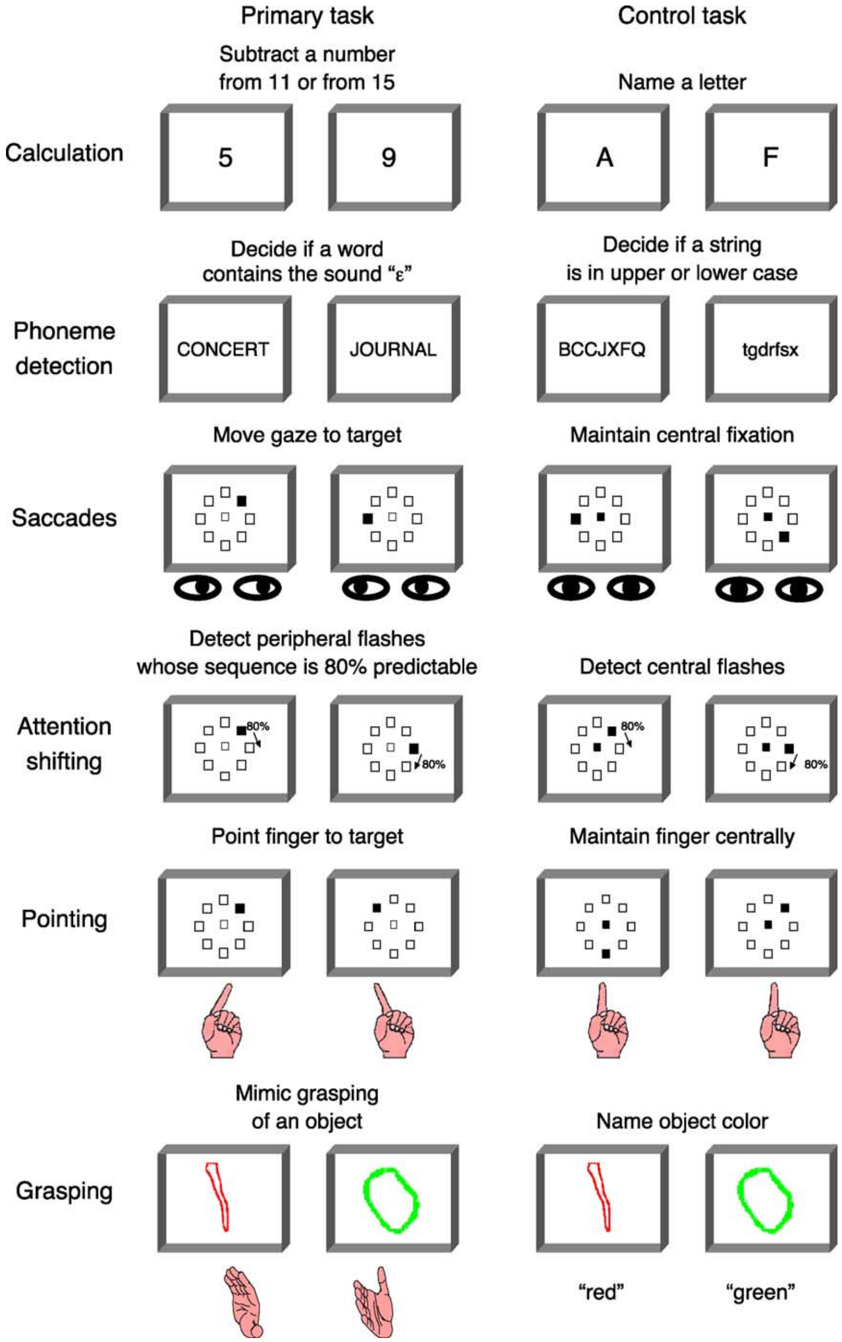

Fig. 1. Schematic depiction of the six pairs of primary and control tasks.

effects model. The group analysis, thresholded at $t < 2.76$ ($P < 0.01$ uncorrected), resulted in six main activation patterns, one for each task, whose spatial distribution has been published (Simon et al., 2002, Fig. 1). Those six patterns were then used as input to the clustering algorithm, which only analyzed voxels activated in at least one task.

Automatized clustering

Clustering methods are useful to many domains including neuroimaging (Duda et al., 2001; Hartigan, 1975; Kaufman and Rousseeuw, 1990). For instance, they have been used to classify similar time series in fMRI data to study functional connectivity and paradigm-related activation (Penny and Friston, 2003) or reproducibility across detection techniques (Goutte et al., 2001). Most previous applications of fMRI data clustering aim at grouping voxels sharing similar time courses, often in the context of single-subject data. In this work, we propose to use clustering to create a partition of the data using summary information from six different task-control pairs collected on a group of 10 subjects.

The summary information chosen is the outcome of the six corresponding SPM analyses. Each of them carries information about the significance of the difference between a task and its control. In order to compare voxels, we use the magnitude of the t statistics, which is a standardized measure of the strength of this differential effect. Since in this particular example all tasks had the same sample size, the *t* statistics is proportional to the Cohen d measure (Cohen, 1988), a well-established standardized summary statistic in the meta-analysis literature. For each voxel, the six *t* values are considered as a multivariate observation, and our goal is to group voxels close to each other in this six-dimensional feature space. We chose the well-known *K*-means clustering method because it is computationally efficient, easy to implement, and requires standard assumptions on the cluster distributions (normality and identity covariances). Note that the method is robust with respect to violation of these assumptions.

The method partitions the data in *K* classes through the optimization of a global criterion, maximizing a measure of similarity within each class and dissimilarity between classes. Each class is represented by its center, in our case the mean of the class observations. The algorithm is unsupervised and is based on the following steps:

1. Initialization: the *K* centers representative of each class are randomly selected in the sample.
2. Assignment: each observation is then assigned to the cluster with a center that is closest to that point.
3. Reestimation: each cluster center is replaced by the mean of all the data points that belong to that cluster.

Steps 2 and 3 are iterated until no observation is reassigned to a different cluster.

Determining the ideal number of classes *K* is a challenging problem for which there is no unanimously accepted criterion. While one may resort to resampling and Monte-Carlo techniques, those methods are inherently computationally very expensive and only provide approximate solutions. If *K* is too large, many classes will resemble each other, while if *K* is too small the class may contain voxels with quite different activity profiles. In our work, we simply tested several values for *K* and retained the one with the simplest interpretation, based on the spatial localization of those classes. The method is therefore supervised and designed only for exploratory analysis of the data (Software will be made available on www.madic.org). In the absence of an automatized criterion for selecting *K*, it must be recognized that our approach remains partially subjective. Further theoretical work, under progress, examines whether simple automatized heuristic rules may render the choice of *K* more objective. However, full automatization is likely to be difficult, because estimates of *K* vary greatly depending on the assumptions of the heuristics used (Schwartz, 1979).

In a previous manual analysis of the same data, focusing solely on the parietal lobe, we had found seven types of significant intersections between the six basic tasks (Simon et al., 2002). Based those results, we expected that $K = 7$ classes would suffice. However, when we tried this value, while the parcellation was overall rather similar to the one presented below, an important difference was that the grasping task did not lead to a distinct class

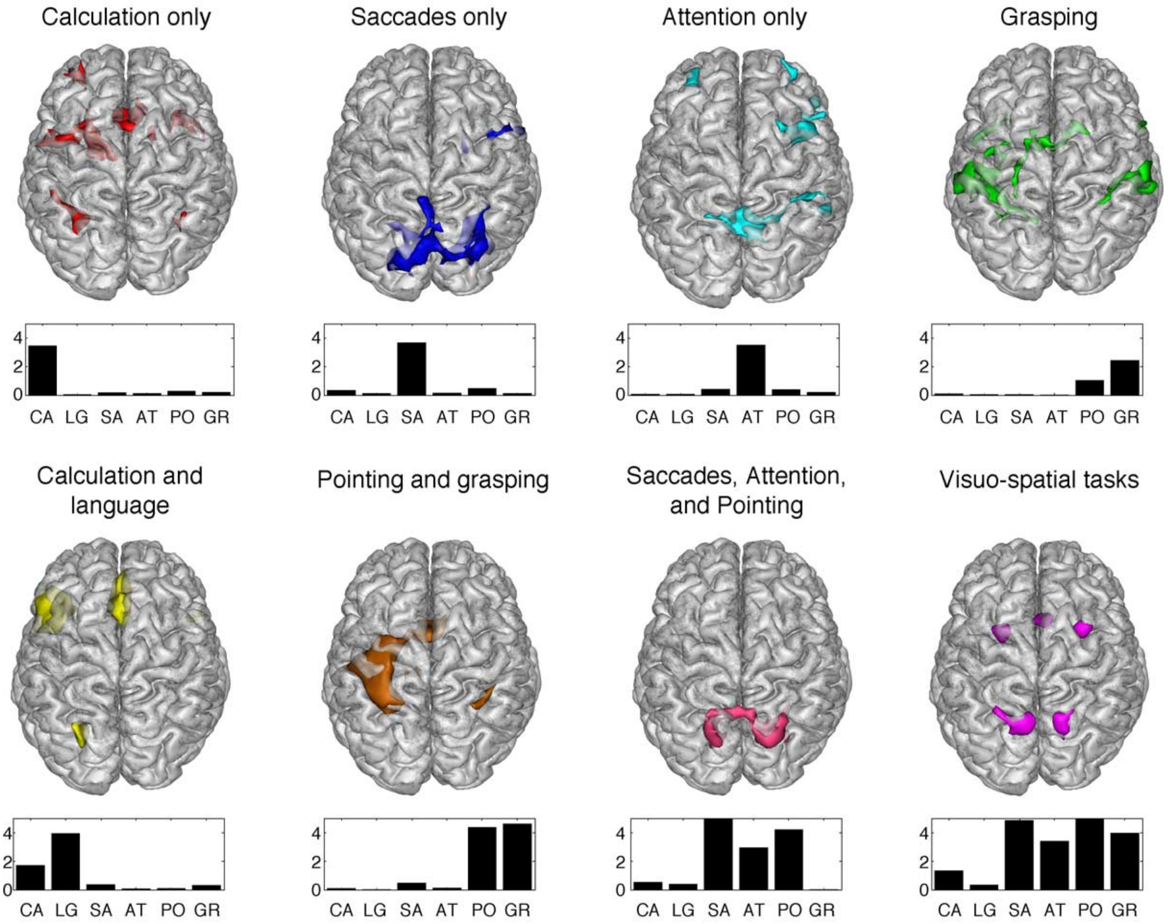

Fig. 2. Three-dimensional glass-brain views of each of the eight classes as well as their typical profile of response to the six tasks (*t* values for primary task superior to control task).

of voxels. Since this was a clear finding in the previous paper, we extended the search to $K = 8$ classes, which gave satisfactory results (see below).

Results

Fig. 2 shows three-dimensional views of each of the eight classes as well as their typical profile of response to the six tasks. In Fig. 3, the eight classes are presented within a single brain volume; axial slices and three-dimensional views provide information about the geometrical relations between the activated voxels. Table 1 summarizes the peak locations and coordinates of the clusters within each class.

The response profile of each class could be easily summarized, in almost all cases, by a strong activation to a subset of tasks and an absence of activation to the other tasks. This is a nontrivial finding, because the algorithm could have detected variable degrees of activation and categorized those as forming a distinct class. Thus, this result suggests that our data can be described as a set of discrete areas, each activated by a small set of tasks.

A second finding is that the observed classes fit well with our previous manual analyses based solely on the parietal lobe. As previously, we observed four sets of regions activated only by a single task: calculation, saccades, attention, and grasping (although the latter was weakly activated by pointing as well) (see Fig. 2, top line). We also observed four sets of regions activated in two or more tasks: calculation and language; pointing and grasping;

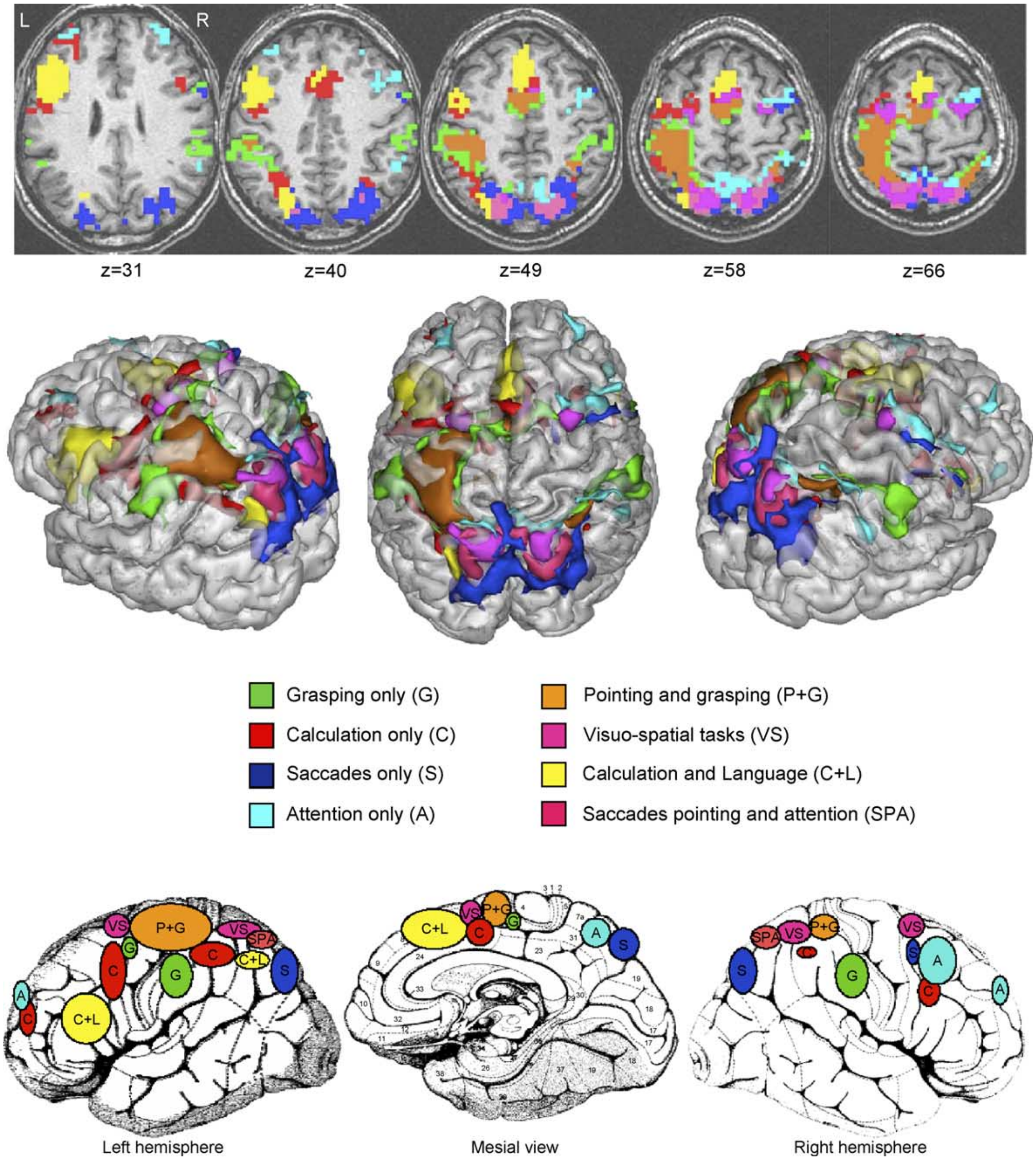

Fig. 3. Axial slices and three-dimensional views of each of the eight classes presented within a single brain volume. The bottom schemas illustrate in a simplified manner the geometrical relations between classes.

Table 1
Peak locations and coordinates of the clusters within each class

Task	Hemisphere	Lobe	Anatomical region	Talairach coordinates		
				x value	*y* value	*z* value
Calculation only	Left	Frontal	Cingular Gyrus	−8	16	36
			Insula	−32	16	8
			Middle Frontal Gyrus	−36	48	24
			Precentral Gyrus	−48	−4	40
			Superior Frontal Gyrus	−28	−8	68
		Parietal	IPS horizontal segment	−38	−56	47
		Deep Grey Nuclei	Putamen	−24	12	4
	Right	Frontal	Cingular Gyrus	4	16	40
			Inferior Frontal Gyrus	40	24	8
			Median Frontal Gyrus	8	16	44
		Deep Grey Nuclei	Caudate Nucleus	16	11	8
Manual tasks only	Left	Frontal	Cingular Gyrus	−4	6	44
			Superior Frontal Gyrus	−5	−4	60
		Parietal	IPS horizontal segment	−36	−44	56
			Postcentral Gyrus	−40	−26	56
			Postcentral Sulcus	−32	−44	64
	Right	Frontal	Superior Frontal Gyrus	8	3	56
		Parietal	Superior Parietal Lobule	36	−44	52
Visuospatial tasks	Left	Frontal	Cingular Gyrus (SEF)	−3	7	52
			Precentral sulcus (FEF)	−25	−4	68
		Parietal	SPL anterior segment	−12	−68	52
	Right	Frontal	Precentral Sulcus (FEF)	28	0	68
			Superior Frontal Gyrus (SEF)	7	5	60
		Parietal	SPL anterior segment	16	−70	56
Saccades only	Left	Parietal	IPTO	−24	−84	24
			SPL posterior segment	−8	−88	36
	Right	Frontal	Precentral Gyrus	62	9	32
			Precentral sulcus	42	−3	56
		Parietal	IPTO	28	−80	24
			IPS posterior segment	28	−64	48
			SPL posterior segment	8	−84	36
		Deep Grey Nuclei	Putamen	23	12	4
Grasping only	Left	Frontal	Inferior Frontal Gyrus	−44	12	12
			Precentral Gyrus	−38	−14	56
			Precentral Gyrus	−56	2	8
			Superior Frontal Gyrus	−6	−7	72
			Superior Frontal Gyrus	−20	−10	80
		Parietal	Postcentral Sulcus	−28	−44	68
			Postcentral Sulcus	−46	−40	40
			Postcentral Sulcus	−60	−32	36
			Postcentral Sulcus	−48	−40	60
	Right	Frontal	Cingular Gyrus	8	4	44
			Precentral Gyrus	62	14	36
			Superior Frontal Gyrus	8	−4	56
			Superior Frontal Gyrus	14	1	72
		Parietal	Postcentral Sulcus	34	−48	60
			Postcentral Sulcus	64	−32	24
Calculation and Language	Left	Frontal	Inferior Frontal Gyrus	−48	20	0
			Inferior Frontal Gyrus	−58	6	20
			Middle Frontal Gyrus	−42	26	20
			Middle Frontal Gyrus	−50	18	28
			Middle Frontal Gyrus	−46	9	44
			Superior Frontal Gyrus	−2	−26	44
		Parietal	IPS posterior segment	−28	−72	44
	Right	Frontal	Inferior Frontal Gyrus	50	21	4
			Superior Frontal Gyrus	6	29	48

(*continued on next page*)

Table 1 (*continued*)

Task	Hemisphere	Lobe	Anatomical region	Talairach coordinates		
				x value	*y* value	*z* value
Attention only	Left	Frontal	Middle Frontal Gyrus	−32	43	36
		Parietal	Precuneus	−5	−62	52
	Right	Frontal	Inferior Frontal Gyrus	52	37	4
			Middle Frontal Gyrus	45	8	52
			Middle Frontal Gyrus	30	38	36
			Precentral Gyrus	54	20	36
		Parietal	IPS/Postcentral Sulcus	44	−40	56
			Precuneus	8	−62	52
			Supramarginal gyrus	60	−44	36
Saccades, Pointing, Attention	Left	Parietal	IPS/Superior Parietal Lobule	−20	−82	44
			Superior Parietal Lobule	−16	−80	48
	Right	Parietal	IPS descending segment	32	−72	36
			Precuneus	8	−66	60
			Superior Parietal Lobule	21	−78	48

saccades, pointing, and attention; and finally, the four visuospatial tasks: grasping, pointing, saccades, and attention (with a weak additional activation during calculation). Only one of the latter classes had not been found in our earlier analysis. We had overlooked a distinction, suggested by the present clustering algorithm, between a network of areas common to the four visuospatial tasks and another neighboring set of parietal areas activated by only three of those tasks (excluding grasping).

Seven of the eight classes comprised both a parietal component and a frontal component. The only exception was the class common to saccades, pointing, and attention whose activations were strictly parietal. In five of eight classes, a mesial frontal/cingulate component was also observed. We now describe the anatomical localization of the clusters in each class. As discussed below, the clusters in each class form plausible long-distance parietofrontal networks, compatible with existing imaging and lesion data, thus reinforcing the validity of the automatized clustering scheme that we used.

Calculation only

Voxels associated with calculation only were observed in a left parietal cluster within the horizontal segment of the intraparietal sulcus. In the frontal lobe, we observed bilateral activation, with a clear predominance in the left hemisphere. In this hemisphere, we observed two clusters of activation, a main one in the precentral gyrus with an extension in the superior frontal gyrus, and the other, much more anterior, in the middle frontal gyrus (Brodmann area 10). In the right hemisphere, we noted small activations in the inferior frontal gyrus (Brodmann area 13) and in the middle frontal gyrus. We also observed a bilateral activation straddling the two hemispheres within the cingular gyrus.

Saccades only

Within the parietal lobe, a large posterior cluster was observed bilaterally during saccades only. This region included superior parietal lobules, posterior segments of the intraparietal sulcus with an extension to the intersection of the intraparietal sulcus, and the transverse occipital sulcus (area IPTO of Wojciulik and Kanwisher, 1999). In the frontal lobe, only two small right-hemispheric clusters were observed, one in the precentral gyrus and the other in the precentral sulcus.

Attention only

The attention task activated specifically multiple regions of the left and right frontal lobe, with a right-hemispheric predominance. While anterior activations in the middle frontal gyrus were bilateral, dorsolateral prefrontal and precentral gyrus activations were found exclusively in the right hemisphere. In the parietal lobe, activations were also predominant in the right hemisphere, with localized clusters in the right supramarginal, right anterior IPS/postcentral sulcus, and midline precunei.

Grasping only

The frontoparietal network observed in this task was bilateral both in the parietal lobe and in the frontal lobe. In the parietal lobe, activations were located at a symmetrical location in the postcentral sulcus extending to the anterior part of the IPS. It should be noted that, aside from these major left and right anterior intraparietal clusters, most clusters were very small and located at the margins of activations common to grasping and pointing. In the left frontal lobe, we detected activation in the inferior frontal gyrus, in the precentral gyrus (two clusters), and in the superior frontal gyrus. In the right hemisphere, frontal activation was localized in the midline frontal cortex, in the superior frontal gyrus, and in the precentral gyrus.

Calculation and language

In the parietal lobe, we observed a small cluster of activation shared between calculation and language in the left posterior segment of the intraparietal sulcus (immediately mesial to the angular gyrus). In the frontal lobe, we observed a large left cluster in the inferior frontal gyrus (pars triangularis and pars opercularis), thus including Broca's area, and extending slightly anteriorly into the middle frontal gyrus. We also observed mesial activation of the superior frontal gyrus, mostly left lateralized but straddling across the two hemispheres. A much smaller cluster of activation was also detected in the right inferior frontal gyrus.

Pointing and grasping

Common to pointing and grasping, we observed a large cluster of activation in the left superior parietal lobule and the upper part of the postcentral gyrus, also extending into the precentral gyrus. We also observed a symmetrical but much smaller cluster in the right superior parietal lobule at the junction between the postcentral sulcus and the intraparietal sulcus. In the frontal lobe, we observed a mesial frontal activation, left lateralized but straddling across the two hemispheres, at a location corresponding to the supplementary motor area.

Saccades, pointing, and attention

Activations common to saccades, pointing, and attention (three tasks that shared the same stimuli) were found only in the parietal lobe. There was a symmetrical activation in the posterior superior parietal lobule, which extended from the precuneus to the posterior border of the IPS. In the right hemisphere, this activation extended slightly into the descending segment of the IPS.

Visuospatial tasks

The four visuospatial tasks (saccades, attention, pointing, and grasping) jointly activated, at symmetrical locations, the convexity of the superior parietal lobule. In the frontal lobe, we also observed symmetrical clusters of activation at the junction of the superior frontal sulcus with the fundus of the superior portion of the precentral sulcus (the classical localization of the frontal eye fields, see Lobel et al., 2001). Finally, there was bilateral mesial frontal activation at a location putatively corresponding to the supplementary eye field (Grosbras et al., 1999; Petit et al., 1996).

Discussion

We have described a simple method for the automatized analysis of intersections between functional brain activation patterns. The main advantage of this method is that, contrary to our previous work (Simon et al., 2002), it does not require experimenter intervention and multiple pairwise comparisons between all the tasks under study. The only manual choices lie in the selection of the statistical threshold and of the number of clusters. The algorithm then automatically detects, across the whole brain volume, voxels that present similar profiles of response and labels them as belonging to similarity classes, thus suggesting that these voxels play a similar functional role.

A limit of the present approach is that it is purely descriptive. The algorithm groups in different classes voxels with maximally different response profiles, but there is no guarantee that those classes are statistically different from each other. However, if two classes consist of data from the same underlying distribution, then it is likely that their center of masse would be distant and their spatial representation not well segregated. The only statistical constraint is that all analyzed voxels pass a test for significant activation in at least one of the six studied tasks (here with a relatively lenient threshold of $P < 0.01$). Thus, the results must be taken as descriptive and as providing guidelines for further research. Nevertheless, several results were of interest.

First, although the algorithm is unconstrained by anatomy or even by proximity of voxels in space, it systematically grouped voxels into relatively large and anatomically meaningful classes, most often forming parietofrontal sets of areas compatible with circuits known from primate neuroanatomy (as further discussed below). Second, the response profiles of the different classes were well differentiated (Fig. 2). It was often the case that the mean t value with a class of voxels was above 3 for some tasks and essentially 0 for others. It is unlikely that such a pattern could be due to chance.

Indeed, a third result is that the present reanalysis uncovered an organization of parietal activations virtually identical to our previous, statistically validated findings (Simon et al., 2002). The only minor difference concerns the activations in the posterior parietal lobule, where the present analysis revealed a further distinction between a cluster common to saccades, pointing, and attention (SPA), and another cluster common to the four visuospatial (VS) tasks of saccades, pointing, attention, and grasping (see Fig. 3). The response profiles of those two regions are strikingly different (Fig. 2), and suggest that the distinction is genuine. The new method thus appears as slightly more sensitive than our previous use of manual intersections between activations. We probably overlooked the posterior parietal distinction because the concerned regions are small and intertwined with each other, thus failing to reach conventional significance for cluster extent. Interestingly, their coordinates roughly correspond with area LIP, which has been identified as a retinotopic area in a delayed saccade task (Sereno et al., 2001). Note that the saccades, pointing, and attention tasks used identical parafoveal stimuli, while the grasping task used a more foveal stimulus (see Fig. 1). Thus, it is possible that the VS and SPA clusters actually correspond to two distinct sectors of a single retinotopic attention map, which would be a tentative human homolog of area LIP.

The main advantage of the present method is to allow for an immediate extension of the parietal analysis to the rest of the scanned volume, including frontal cortex. This allowed us to identify frontal regions with a response profile paralleling that of the parietal regions that we had previously reported. Tentatively, these shared parietofrontal profiles of activity can be compared to the large-scale interconnected parietofrontal networks, as observed in primate neuroanatomical studies (Pandya and Yeterian, 1990; Rizzolatti et al., 1998). In both macaque and humans, the same global geometry seems to be found. Two large-scale symmetry principles were observed in the present data (see Fig. 3):

- Preserved dorsal–ventral organization: on a dorsal-to-ventral axis, the same ordering of activations is observed in the lateral parietal, lateral prefrontal, and mesial prefrontal regions. The visuospatial and manual activations systematically occupy more dorsal sectors, while calculation and language-related activations occupy more ventral sectors.
- Anteroposterior symmetry around the central sulcus: whenever two regions are separated in the parietal lobe and two regions with similar response profiles are identified in the frontal lobe, the ordering of those activations along an anteroposterior axis is reversed. For instance, in the parietal lobe, the intersection of calculation and language falls posterior to the activation for calculation only. In frontal cortex, this relation is reversed: in both lateral and mesial frontal areas, calculation is more posterior than the calculation and language cluster. A similar parietofrontal reversal is observed for clusters related to visuospatial and to manual tasks.

As a corollary of those two principles, five areas of activation tend to entertain systematic topological relations in parietal, lateral frontal, and mesial frontal cortex: grasping only, manual tasks, visuospatial tasks, calculation only, and calculation and language (see Fig. 3). This large-scale symmetrical organization may reflect evolutionary constraints on the progressive architectonic differentiation of the cerebral cortex, as suggested initially by Pandya and Yeterian (1990). It suggests, in particular, a coordinated expansion of the inferior parietal lobule and of the inferior frontal lobe, including Broca's area, in support of language and mathematical abilities that have seen a major expansion in recent human evolution (Eidelberg and Galaburda, 1984). In support of this hypothesis, emerging quantitative studies of relative cortical surface in macaques and humans suggest a considerable differential expansion of those regions in humans relative to macaques (Van Essen et al., 2001).

Two factors complicate this overall pattern of parietofrontal symmetries. First, some functions are strongly lateralized in humans. Indeed, clusters relating to calculation and to language are found mostly in the left hemisphere, while clusters relating to attention orienting are found mostly in the right hemisphere. Those asymmetries are particularly pronounced in the lateral frontal lobe (Fig. 3). The right-hemispheric predominance of the attention task is in good agreement with the literature on attention and neglect (Mesulam, 1981), while the left lateralization of language and calculation processes is of course consistent with that of a century of neuropsychological research.

Second, some parietal clusters have little or no equivalent in the frontal cortex. In particular, we observed posterior parietal clusters for saccades only, and for saccades, pointing, and attention, whose response profiles were essentially absent in frontal cortex. Similarly, grasping only was associated with large bilateral clusters in the anterior IPS, but with only a few isolated voxels in the frontal lobes. Overall, those results tentatively suggest a trend toward the representation of more abstract and less effector-specific functions in the frontal lobe relative to the parietal lobe.

The most striking example of this frontal trend toward abstraction lies in the response of the frontal eye fields. A strong saccade-related activation was observed at the classical location of the FEF, namely the intersection of the superior frontal and precentral sulci (Lobel et al., 2001). However, this activation was entirely shared with attention, pointing, and grasping tasks in which subjects did not move their eyes. This result suggests a more abstract attention-related function for the FEF proper, as proposed by many others (Corbetta et al., 1998; Gitelman et al., 1996, 1999; Lang et al., 1994). For instance, Gitelman et al. (1996) studied regions involved in nonvisual exploratory motor aspects of attention (subjects explored a surface with the right hand to identify targets or performed a repetitive circular motion). Activations were strictly right-lateralized and located in the posterior parietal cortex, the premotor, and the anterior cingulate cortex, suggesting that this motor attention paradigm activated structures also involved in visual attention and saccades. Similarly, in the posterior parietal lobe, Wojciulik and Kanwisher (1999) observed an overlap of activations during three different forms of attention: peripheral attention shifting, sustained attention to parafoveal locations, and temporal attention to feature conjunctions. It is thus likely that this set of regions, although easily activated by saccades, plays a much more abstract role in the movement of attention on various external and internal continua.

By contrast with this complex overlap, activations relating strictly to eye movements were observed only in the posterior parietal region as well as in a right lateral precentral region that corresponds to the site of a second previously described oculomotor area (Lobel et al., 2001).

Turning now to manual tasks, we initially speculated that the human anterior region specific for grasping and located in the supramarginal/postcentral region could be tentatively related to monkey area AIP, located in the rostral part of the lateral bank of the intraparietal sulcus (Simon et al., 2002). The present results indicate that responses parallel to those of this parietal area are present in the left inferior frontal and precentral gyrus. Overall, these regions may constitute a human equivalent of the monkey circuit linking areas AIP and F5, as suggested by previous imaging and lesion data (Binkofski et al., 1999; Buccino et al., 2001).

Concerning mental arithmetic, the present results confirm that two distinct anatomical systems of areas are involved (Dehaene and Cohen, 1995; Dehaene et al., 2003). The first one, involving the angular gyrus and Broca's area, is shared with language processing and is engaged especially during rote memory tasks such as fact retrieval (e.g., multiplication tables) (Delazer et al., 2003; Lee, 2000). The second one, involving the horizontal segment of the intraparietal sulcus and the precentral gyrus, involves a nonlinguistic representation of quantity and is especially activated by numerical comparison, subtraction, and approximation tasks (Dehaene et al., 1999, 2003; Pinel et al., 2001, 2004). The present results closely replicate the localizations of those two sets of areas, whose frontal and parietal components are presumably interconnected by direct projection pathways.

Recently, a possible precursor of the human quantity system has been identified in the monkey. In two animals trained with a numerosity match-to-sample task, Nieder and Miller (2003) and Nieder et al. (2002) recorded neurons tuned to a specific number of visual objects. Importantly, while these "number neurons" were initially found in the prefrontal cortex (areas 45, 46, and 10), another population with an earlier latency has been observed in the fundus of the intraparietal sulcus, close to area VIP (Nieder and Miller, 2004), which is a plausible homolog of the human quantity-related IPS activation. In the monkey, VIP entertains strong connections to premotor area F4 (Rizzolatti et al., 1998). In accordance with this projection scheme, in the present study as well as in previous work in human fMRI (Dehaene et al., 2003; Pinel et al., 2001, 2004), we found a strong precentral activation paralleling the deep IPS activation during calculation. This precentral site thus appears as a plausible human homolog of F4. Although clearly speculative, this monkey–human homology makes the simple prediction that neurons tuned to number might also be found if recordings were made in monkey F4.

Overall, the large-scale geometrical parietofrontal organization found for eye and hand movements as well as for language and arithmetic suggests that the cortical location of both cognitive and sensorimotor functions might be subsumed by a few broad principles that might affect the entire parietal and precentral regions during development. One such principle is somatotopy (Buccino et al., 2001; Schubotz and von Cramon, 2003). In that respect, it is striking that the present calculation and language activations are in register, respectively, with the finger and mouth sites of parietal and precentral somatotopic maps. In brain-lesioned patients, acalculia is often associated with loss of finger knowledge in Gerstmann's syndrome, while aphasia is often associated with apraxia of speech and other articulation deficits. Thus, the development of human areas for arithmetic and language may emerge, in phylogeny or ontogeny, from precursor areas engaging the corresponding motor effectors.

Conclusions

We have reported a global topographical geometry of functional parietofrontal networks in humans. An important suggestion of the present work is that insertion of human cognitive functions for calculation and language does not deviate from the functional topography of sensorimotor activations, but follows similar rules of topographic parietofrontal projection and symmetry around the central sulcus.

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