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Event-related fMRI analysis of the cerebral circuit for number comparison

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CEREBRAL activity during number comparison was studied with functional magnetic resonance imaging using an event-related design. We identified an extended network of task-related areas that showed a phasic activation following each trial, including anterior cingulate, bilateral sensorimotor areas, inferior occipitotemporal cortices, posterior parietal cortices, inferior and dorsolateral prefrontal cortices, and thalami. We then tested which of these areas were affected by number notation, numerical distance and response side, three variables that specifically target processes of visual identification, quantity manipulation and motor response in a serial-stage model of the number comparison task. Our results confirm the role of the right fusiform gyrus in digit identification processes, and of the inferior parietal lobule in the internal manipulation of numerical quantities. *NeuroReport* 10:1473–1479 © 1999 Lippincott Williams & Wilkins.

Key words: Arithmetic; Distance effect; Fusiform gyrus; Parietal cortex

Introduction

Brain imaging techniques often reveal a large network of cerebral areas involved in a cognitive task. Assigning a precise function to each of these activated areas, however, can be difficult. Here, we address this issue using an extension of the logic of additive factors [1,2]. By selectively manipulating orthogonal parameters of the stimulus set, and identifying which brain areas are implied in processing each parameter, we provide a functional decomposition of the active network. This strategy was applied to a simple number comparison task, in which subjects decide whether a visually presented number is larger or smaller than 5. Models of this task [2–6] decompose it into three successive stages of visual identification (affected by the notation of the stimuli, Arabic or verbal), magnitude comparison (affected by the distance between the number and 5), and response elaboration and execution (affected by the hand used for responding). A previous event-related potential (ERP) study of this task [2] suggested a temporal and spatial localization of these processes. Visual identification was hypothesized to involve the ventral occipito-temporal region at about 150 ms post-stimulus, bilaterally for Arabic numerals (e.g. 4) and with a left lateralization for verbal numerals (e.g. FOUR). Magnitude comparison involved the left and right inferior parietal regions at about 180 ms post-stimulus, while motor processes were related to the left and right motor cortices starting about 140 ms before the key press.

We examined whether these tentative localizations could be confirmed with the anatomically accurate method of functional magnetic resonance imaging (fMRI). Using an event-related design [7] and a statistical analysis capable of detecting any change in the size, shape or amplitude of the blood flow response in local regions, we were able to detect small parameter-dependent effects which were not seen with a more standard method based on statistical parameter mapping (SPM).

Materials and Methods

Subjects: Subjects were 11 healthy volunteers (two women and nine men; mean age 25.7 years), who gave their written informed consent. All subjects were right-handed according to the Edinburgh inventory. The protocol was approved by an institutional ethical committee for biomedical research.

Stimuli: An event-related design was used. A list of 128 randomly intermixed stimuli was presented through mirror glasses and an active matrix video projector (EGA mode, 70 Hz refresh rate), with a 14 s inter-stimulus interval. The fMRI images analyzed here result from a masked priming experiment [8]. Stimuli consisted in an initial random letter string (duration 71 ms), then a numerical prime

(43 ms), another random letter string (71 ms), and finally a target number (200 ms). The subject was asked to decide whether the target number was larger or smaller than 5 by pressing a button with his right or left hand. Subjects performed two blocks of 32 trials with the larger response assigned to the right hand, and two blocks to the left hand, in random order. Here, we limit our investigations to the cerebral activation associated with three parameters of interest: the notation of the target (verbal or Arabic) ; its distance from 5 (two targets were close (4 and 6), and two were far (1 and 9)); and its accompanying motor response (right or left hand). These are the same parameters that were studied in an earlier ERP study of number comparison [2]. The prime number varied orthogonally to the target number, following the same parameters. Its effects have been described in part elsewhere [8]. Since this masked prime was not consciously seen by the subjects, and since its effects were very small, they are not studied in the present report, which is more specifically dedicated to the comparison task.

Image acquisition: On each trial, stimulus onset was synchronized with the acquisition of the first slice in a series of seven volumes of 18 slices each (one volume every 2 s). We used a gradient-echo echo-planar imaging sequence sensitive to brain oxygen-level dependent contrast (18 contiguous axial slices, 6 mm thickness, TR/TE = 2000/40 ms, in-plane resolution $3 \times 4\,\mathrm{mm}^2$, 64×64 matrix) on a 3 T whole body system (Bruker, Germany). High-resolution anatomical images (3D gradient-echo inversion-recovery sequence, T1 = 700 ms, TR = 1600 ms, FOV = $192 \times 256\,\mathrm{mm}^2$, matrix = $128 \times 128 \times 256$, slice thickness = 1 mm) were also acquired.

Image analysis: Analysis was performed with statistical parameter mapping software (SPM96: http://www.fil.ion.ucl.ac.uk/spm). Images were corrected for subject motion, normalized to Talairach coordinates [9] using a linear transform calculated on the anatomical images, and smoothed (FWHM = 15 mm). For each subject, correct trials were averaged together separately for each level of target distance, notation and response side. Thus, the data were reduced to eight average trials for each subject, each consisting of seven consecutive volumes spanning the 14 s interval following each stimulus (for a total of 56 average volumes per subject). The average images from all 11 subjects were then analyzed together. The generalized linear model was used to model the intensity level of each pixel as a linear combination, for each subject and each trial type, of two activation function with hemodynamic lags of 4 and 7 s, thus allowing for differences in acquisition and activation times across slices and brain regions. Three types of statistics were performed. For SPM-based identification of overall task-related cerebral activity, we first determined the areas that showed a transient increase in activation following stimulus presentation, as identified by a significant positive correlation with the hemodynamic functions. For SPM-based contrast analysis, we then used a contrast analysis to identify areas affected by our experimental variables. Statistical maps were formed for each of six contrasts of interest (Arabic *vs* verbal for the notation effect, close *vs* far for the distance effect, right *vs* left for the response side effect). A voxel-wise significance level of 0.001, corrected to $p < 0.05$ for multiple comparisons across the brain volume, was used. We also used an uncorrected significance level of 0.001 to test specific contrasts with a strong anatomical *a priori* hypothesis: notation effects within the left and right ventral occipito-temporal pathways, and distance effects within the left and right parietal lobe. For single-voxel temporal profile analysis, we searched the entire circuit of active areas for notation, distance, and response side effects. All 47 local maxima identified in the first step, with a Z score > 8 ($p < 5 \times 10^{-15}$) were selected. In each of these voxels, an analysis of variance (ANOVA) was applied to the average fMRI signal with notation, distance, response side and time as within-subject factors. Significant effects were identified by testing the interaction terms notation × time, distance × time, and response side × time. We report all significant differences with $p < 0.05$ (corrected with the Greenhouse-Geisser method).

Results

Task performance: An ANOVA on correct reaction times (RT) showed main effects of distance ($F(1,10) = 26.6$, $p = 0.0004$; close 28 ms slower than far) and notation ($F(1,10) = 11.3$, $p = 0.0072$; verbal 18 ms slower than Arabic). The effect of response side did not reach significance ($F(1,10) = 0.34$, $p = 0.575$; left 3 ms slower than right). There was no interaction of these variables, in good agreement with previous results and with the proposed serial-stage model of comparison. Error rate averaged 1.8% and was not affected by any of these variables.

Overall task-related cerebral activity: The entire circuit of areas showing a significant transient increase in activation following stimulus presentation is shown in Fig. 1 and Table 1. It should be noted that the amplitude of the activation was not always correlated with its significance, as assessed by the SPM Z-score. The areas where the percentage acti-

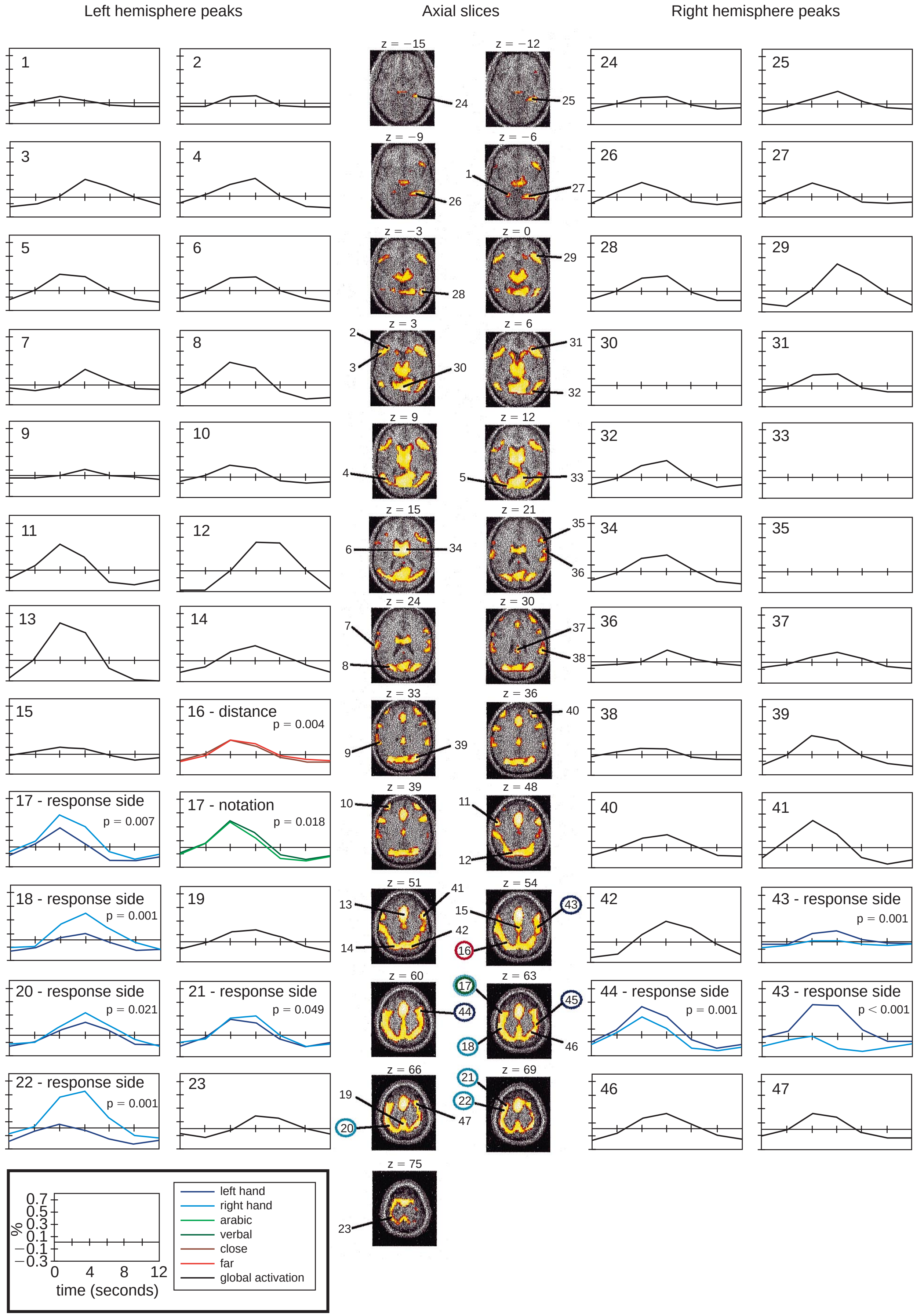
Left hemisphere peaks
Axial slices
Right hemisphere peaks
1
2
z = −15
z = −12
24
25
3
4
z = −9
z = −6
1
26
27
5
6
z = −3
z = 0
28
29
7
8
z = 3
z = 6
2
3
30
31
32
9
10
z = 9
z = 12
4
5
33
32
33
11
12
z = 15
z = 21
6
34
35
36
34
35
13
14
z = 24
z = 30
7
8
37
38
36
37
15
16 - distance
p = 0.004
z = 33
z = 36
9
39
40
38
39
17 - response side
p = 0.007
17 - notation
p = 0.018
z = 39
z = 48
10
11
12
40
41
18 - response side
p = 0.001
19
z = 51
z = 54
13
14
41
42
15
16
43
42
43 - response side
p = 0.001
20 - response side
p = 0.021
21 - response side
p = 0.049
z = 60
z = 63
17
44
18
45
46
44 - response side
p = 0.001
43 - response side
p < 0.001
22 - response side
p = 0.001
23
z = 66
z = 69
19
20
21
22
47
46
47
z = 75
23
0.7
0.5
0.3
0.1
−0.1
−0.3
%
0
4
8
12
time (seconds)
left hand
right hand
arabic
verbal
close
far
global activation

Table 1. Talairach coordinates and Z-score of the 47 most significantly activated voxels with a Z-score > 8, during the number comparison task. Graph numbers correspond to Fig. 1.

Graphic n°	Brain area	x=	y=	z=	Z
34	*Thalamus*	9	−6	15	10.21
13	*Anterior cingulate gyrus*	0	15	51	10.15
6	*Thalamus*	−12	−9	15	9.87
41	*Middle frontal gyrus*	51	9	51	9.79
46	*Postcentral gyrus*	36	−45	63	9.72
5	*Middle occipital gyrus*	−27	−81	12	9.68
8	*Middle occipital gyrus*	−30	−75	24	9.68
30	*Internal occipital gyrus*	0	−72	3	9.67
39	*Superior occipital gyrus*	30	−69	33	9.67
44	*Middle frontal gyrus*	42	3	60	9.64
22	*Precentral gyrus*	−39	−18	69	9.61
28	*Middle occipital gyrus*	48	−63	−3	9.6
12	*Precuneus*	−6	−72	48	9.59
17	*Precentral gyrus*	−45	−6	63	9.52
18	*Postcentral gyrus*	−48	−27	63	9.52
20	*Superior parietal lobule*	−42	−42	66	9.52
16	*Superior parietal lobule*	−33	−54	54	9.5
4	*Inferior temporo-occipital gyrus*	−51	−66	9	9.48
11	*Middle frontal gyrus*	−54	9	48	9.45
31	*Inferior frontal gyrus*	36	33	6	9.44
47	*Superior frontal gyrus*	30	3	66	9.44
29	*Inferior frontal gyrus*	54	24	0	9.4
42	*Precuneus*	12	−72	51	9.4
21	*Superior frontal gyrus*	−33	0	69	9.39
33	*Posterior cingulate gyrus*	12	−60	12	9.38
14	*Precuneus*	−21	−72	51	9.33
40	*Superior frontal gyrus*	33	51	36	9.3
25	*Fosiform gyrus*	45	−48	−12	9.27
19	*Precuneus*	0	−51	60	9.25
45	*Precentral gyrus*	39	−15	63	9.21
27	*Fusiform gyrus*	24	−57	−6	9.07
10	*Middle frontal gyrus*	−39	45	39	9.06
32	*Middle occipital gyrus*	36	−78	6	9.05
37	*Posterior cingulate gyrus*	0	−24	30	9.04
26	*Fosiform gyrus*	30	−51	−9	8.98
3	*Inferior frontal gyrus*	−60	18	3	8.9
38	*Inferior parietal lobule*	60	−30	27	8.88
24	*Fusiform gyrus*	39	−39	−15	8.84
35	*Inferior frontal gyrus*	60	18	21	8.67
2	*Inferior frontal gyrus*	−39	30	3	8.66
43	*Postcentral gyrus*	45	−24	54	8.5
23	*Postcentral gyrus*	−27	−45	75	8.49
15	*Cingulate gyrus*	0	−24	54	8.44
7	*Precentral gyrus*	−69	−15	24	8.37
36	*Postcentral gyrus*	66	−9	21	8.27
1	*Parahippocampal gyrus*	−24	−51	−6	8.17
9	*Inferior parietal lobule*	−60	−30	33	8.1

vation changes were the largest included the anterior cingulate, bilateral sensorimotor areas, occipital pole, posterior parietal cortex/precuneus, and inferior and dorsolateral prefrontal cortex, with a tendency to a greater activity in the right inferior frontal gyrus than in the left. Smaller activation was seen in the right and left thalami, temporo-occipital junctions, intraparietal sulci and the right fusiform gyrus.

Contrast analysis: At the standard level of significance, only response side showed a significant effect in SPM. The active areas were strictly contralateral

FIG. 1. Map of the significant variations in BOLD signal, averaged across trials and subjects. Central column, axial slices from the base to the top of the brain. Colors indicate significant areas at a voxelwise significance level of 0.001, corrected to $p < 0.05$ for multiple comparisons across the brain volume. Note that averaging across subjects and smoothing of the BOLD images occasionally resulted in a smearing of activations, particularly along the ventricles. Some geometrical deformation, due to the known impact of static magnetic field inhomogeneities on EPI images [26], is also perceptible in the occipital lobe. Only the slices containing a significant peak with Z-score > 8 ($p < 5 \times 10^{-15}$) are shown. The left and right graphs show the temporal dynamics of the BOLD signal at each of these activation peaks. A single black curve is shown if no effect was detected by ANOVA in the considered voxel. Otherwise, two colored curves indicate the activation profile in each corresponding condition (see color legend at bottom left). In this case, the ANOVA-based p value is indicated, as well as the name of the effect.

to the response hand, comprising the right sensorimotor cortex (Talairach coordinates (TC) 39, −15, 63; Z = 9.18), right supplementary motor cortex (TC 9, −6, 57; Z = 6.47) and right central/insular cortex (TC 42, −9, 24; Z = 6.53) for left-hand responses and symmetrical areas (TC −39, −18, 66; Z = 8.81; TC −9, −9, 57; Z = 6.81; TC −45, −12, 24; Z = 5.74) for right-hand responses. At uncorrected $p < 0.001$, the anatomically constrained analysis identified notation and distance effect (see Fig. 2). A small area of the right fusiform gyrus was significantly more activated by Arabic digits than by verbal numerals (TC 54, −51, −6; Z = 3.62; 13 voxels). Conversely, no ventral occipito-temporal area was significantly more activated for verbal than for Arabic notation. As for distance effects, a left inferior parietal area close to the parieto-occipito-temporal boundary was significantly more active for numbers close to 5 than for numbers far from 5 (TC −48, −66, 21; Z = 3.59; 17 voxels). Conversely, a right intraparietal area was significantly more active for far than for close numbers (TC 48, −36, 39; Z = 3.89; 28 voxels).

Single-voxel temporal profile analysis: The 47 identified activation maxima (see Materials and Methods and Fig. 1) were distributed evenly within the network of active areas, thus allowing us to test for notation, distance, and response side effects at various places throughout this network. Number notation affected the activation profile in the left precentral gyrus. Activation appeared to last longer for verbal than for Arabic numerals (Fig. 1, box 17). A distance effect was found in the left intraparietal sulcus (Fig. 1, box 16), where numbers close to 5 yielded a slightly earlier activation peak than numbers far from 5. Finally, response side affected many sites distributed bilaterally in precentral and postcentral cortices.

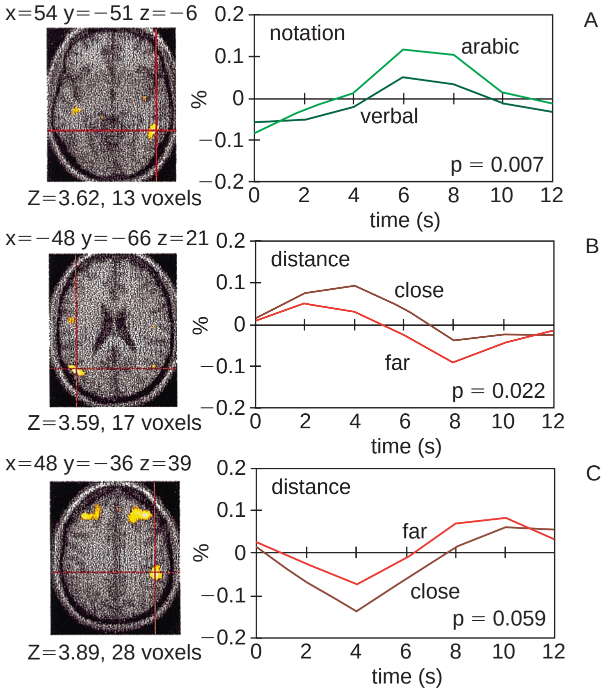

FIG. 2. Brain slices where the anatomically constrained contrast analysis revealed a significant notation or distance effect. For visualization purpose, the image was thresholded at $p < 0.01$, but an uncorrected threshold of $p < 0.001$ was used to detect significant activations, here appearing at the intersection of the two red lines. Graphs on the right side represent the BOLD signal, with an ANOVA analysis of the voxel (see corresponding legend to Fig. 1). (**A**) Arabic–verbal contrast, right fusiform gyrus. (**B**) Close–far contrast, left inferior parietal area. (**C**) Far–close contrast, right intraparietal area.

Discussion

We used event-related fMRI to analyze an extended circuit of brain areas activated phasically during number comparison. In addition to the bilateral parietal activation, which was previously known to be involved in various number processing tasks [10–12], this circuit included visual and motor cortical areas as well as prefrontal and anterior cingulate cortices. Our event-related design allowed us to visualize the amplitude and shape of the hemodynamic response in each of these regions. The amplitude of the BOLD response varied considerably between different areas. For instance, the response of the thalamus was about three times smaller than that of the anterior cingulate, although both figured amongst the most significantly activated areas. At this point, however, it is difficult to disentangle the potential causes of this effect, which may include differences in vascularization, hemodynamics, and the size of the active neuronal popoulations. The activated areas also responded with different delays. Although the order in which the slices were acquired (interleaved slices, from the bottom to the top of the brain) could have induced artefactual delays [13] of up to 2 s, some of the variations in activation delays seen in Fig. 1 exceed this value, suggesting that they may partly reflect genuine inter-area differences in the shape of the BOLD response [14]. Further research, using corrections for acquisition delays, should sort out the respective contributions of neural activation delays and/or local variations in the coupling of activation to blood flow to this effect.

Considering these variations in amplitude and delay, we used an ANOVA-based statistical analysis capable of detecting any task-induced change in the shape of the BOLD response of a given voxel. Using the general linear model underlying SPM software, one can only detect changes in the amplitude of the weights allocated to prespecified model hemodynamic functions. On the contrary, an ANOVA applied directly to the event-related BOLD signal can potentially detect any interaction of an experimental condition with the time factor, and thus any change in the lag, size and shape of the BOLD response due to experimental factors. One difficulty raised by this type of study is the selection of the voxels which are analyzed with the ANOVA. The choice of the most significantly activated voxels allowed us to analyze only a limited number of voxels dispersed throughout the cortex and which provided a good description of the cerebral circuit involved in the task. However, because we did not apply a statistical correction for the number of tests performed (three tests at each of 47 voxels), our results should be considered as exploratory.

The combined application of this strategy and of traditional SPM contrast analysis allowed us to identify candidate areas for number notation, distance and response effects. First, a robust effect of number notation was found in the right fusiform gyrus. This area is more activated by digits than by number words. This suggests that within the ventral occipito-temporal pathway for visual identification, there may exist a right-hemispheric area specialized for the visual recognition of digits as opposed to words. This region may be homologous to the visual word form system of the left hemisphere [15]. Several other published observations corroborate the hypothesis of two different neural systems for Arabic and verbal identification. Recordings of local field potentials in human extrastriate visual cortex [15] have revealed a ventral area more reactive to digits than to words or faces in the fusiform gyrus, suggesting the existence of a number module specifically sensitive to digit forms. Furthermore, the right hemisphere of patients with callosal lesions can recognize digits, but not number words [16,17], confirming the crucianumber module specifically sensitive to digit forms. Furthermore, the right hemisphere of patients with callosal lesions can recognize digits, but not number words [16,17], confirming the crucial role of the left hemisphere for visual word identification and the capacity of the right hemisphere to identify digits. Finally, a study of the comparison task with ERP recordings [2] has suggested a left hemispheric identification process for words and a bilateral identification process for digits, both of which later converge onto a common amodal magnitude representation. Our results are compatible with this model, and suggest that the right fusiform gyrus may play a special role in recognizing Arabic digits during number comparison.

We also noticed a small notation effect in the left precentral gyrus. Interestingly, the very same voxel was also affected by a large effect of response side. It is unlikely that the same brain area is involved in visual identification and motor processes. Rather, the shape of the notation effect is indicative of a differential delay in motor activation between the two conditions, with a longer activation for verbal notation than for Arabic notation. Analysis of reaction times indicated that subjects responded 18 ms slower to verbal than to Arabic numerals. It is then possible that the apparent notation effect observed in the BOLD response of this premotor voxel was simply related to the delayed motor activation of this region due to a longer processing of verbal stimuli. This interpretation would require a replication to be validated, however, because it seems somewhat surprising that such a small response time difference may be measurable at the level of the hemodynamic response.

We also reported a distance effect, independent of notation and response side, in three different sites: two in the left inferior parietal lobule, and one in the right postcentral/inferior parietal region. This bilateral inferior parietal effect is in good agreement with the assumption of an abstract representation of number magnitude in this area [18]. Our data suggest that the lateralization of this magnitude representation is perhaps more complex than expected. Indeed, we found here the most significant distance effect in the left hemisphere, whereas a previous ERP experiment suggested a right-hemispheric advantage [2]. In both left and right parietal areas, however, number notation was found irrelevant. While verbal and Arabic notations are identified by partially distinct inferior temporal areas, as discussed previously, parietal cortices may constitute converging points where the common semantic information conveyed by both notations is represented.

Finally, we observed the expected effect of response side over a large set of left and right sites surrounding the central sulcus, as well as in the supplementary motor area (SMA) and in the insula. Pre- and post-central sensorimotor areas were systematically more activated for contralateral than for ipsilateral hand movement. Globally, these data are in good accordance with the proposed theoretical model of the task, which postulates a visual identification of numbers in the left and right ventral occipito-temporal areas, a bilateral magnitude representation in the inferior parietal lobule, and the implementation of the appropriate response in motor areas.

In addition to comparison itself, the design of our experiment probably called on other cognitive capacities. First, the fast detection of the target number probably required focused visual attention throughout the experiment. Second, the target had to be compared with a fixed reference number (five) which was memorized, probably requiring the use of working memory resources. Third, the motor response instructions changed between blocks, which required subjects to inhibit a previously automatized task and therefore put requirements on higher-level control processes. Fourth, subjects made occasional errors and presumably used error detection and correction processes on those trials. Those factors may explain our finding of widespread activation in prefrontal, parietal, cingulate and subcortical areas which may not be specifically related to number comparison. Prefrontal cortex and anterior cingulate, in particular, are considered as crucial areas for the high-level control of activity and task switching. Anterior cingulate activation is found in many effortful tasks [19] that require attention for action [20] and involve the monitoring of conflicting responses [21] and the correction of occasional errors [22]. Prefrontal cortex may be related to a supervisory attentional function [23] of controlling lower-level sensorimotor processes. Finally, the lateral prefrontal activations, in connection to the parietal activations (at sites where no distance effect was found), may be indicative of the involvement of working memory for the reference number and task instructions [24,25].

Conclusion

In conjunction with a previous ERP study of the same task, the present study provides evidence that an organized sequence of cerebral activations underlies the number comparison task. Thanks to the event-related fMRI method, the size, lag and temporal shape of the activations can now be visualized. The complexity of the distributed cerebral network implicated in this simple cognitive task reinforces the idea that any psychological ability results from the coordinated activity of multiple specialized cerebral systems, rather than from the operation of a single dedicated brain area. The variant of the additive-factors method proposed here, which involves the orthogonal variation of multiple stimulus parameters and the examination of their impact on each brain area, provides a general means of defining the function of these distributed subsystems.

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