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Cerebral activations during number multiplication and comparison: a PET study

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Abstract—Positron emission tomography was used to examine the cerebral networks underlying number comparison and multiplication in eight normal volunteers. Cerebral blood flow was measured within anatomical regions of interest defined in each subject using magnetic resonance imaging. Three conditions were used: rest with eyes closed, mental multiplication of pairs of arabic digits and larger–smaller comparison of the same pairs. Both multiplication and comparison activated the left and right lateral occipital cortices, the left precentral gyrus, and the supplementary motor area. Beyond these common activations, multiplication activated also the left and right inferior parietal gyri, the left fusiform and lingual gyri, and the right cuneus. Relative to comparison, multiplication also yielded superior activity in the left lenticular nucleus and in Brodmann's area 8, and induced a hemispheric asymmetry in the activation of the precentral and inferior frontal gyri. Conversely, relative to multiplication, comparison yielded superior activity in the right superior temporal gyrus, the left and right middle temporal gyri, the right superior frontal gyrus, and the right inferior frontal gyrus. These results underline the role of bilateral inferior parietal regions in number processing and suggest that multiplication and comparison may rest on partially distinct networks. Copyright © 1996 Elsevier Science Ltd.

Key Words: cerebral blood flow; positron emission tomography; parietal cortex; acalculia.

Introduction

In the last decade, considerable progress has been made towards understanding the mental architectures for number processing. Cognitive neuropsychological studies of brain-lesioned patients with arithmetical deficits have been instrumental in developing models of number comprehension and production, and of the operations involved in mental calculation [5, 9, 15, 40, 41]. Most studies, however, have focused almost exclusively on the functional organization of mental arithmetic rather than on its anatomical substrate. Hence, although detailed functional models of number processing are now available, our knowledge of the cerebral bases of mental arithmetic remains weak.

A few studies have used brain-imaging techniques in normal subjects to measure cerebral blood flow during number processing. In a pioneering experiment, Lennox [37] observed an increase in the oxygen saturation of blood drawn from the jugular vein during mental arithmetic as opposed to rest. Sokoloff *et al.* [48], however, found little effect of mental arithmetic on global cerebral blood flow. More recently, Roland and Friberg [46], using the ^{133}Xe technique, observed activations in the left and right angular gyri and prefrontal cortex during performance of a continuous subtraction task which involved repeatedly subtracting three from some initial number (e.g. 50, 47, 44, 41, etc.). Appolonio *et al.* [2], using a similar task with fMRI, also reported inferior parietal and lateral frontal activations.

None of these studies, however, have attempted to determine the specific contributions of different brain areas to number processing. From a cognitive viewpoint, the continuous subtraction task probably involves many different processes such as arithmetic fact retrieval, carrying, or verbal working memory, and it is unclear which of these processes are responsible for the observed bilateral

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inferior parietal and frontal activations. As a first step towards addressing this issue, the present study attempted to specify in greater detail the cerebral networks implicated in two much simpler number-processing tasks, single-digit multiplication and comparison. Pairs of digits were flashed, one at a time, and subjects were told either to compute their product, or to select the larger of the two digits. Our primary goal was to study whether the inferior parietal cortex would be activated in either or both tasks. We examined also whether the activation of other areas differed between the two tasks.

Methods

Subjects

Eight right-handed French healthy male medical students participated to this study. Mean subject age was 24.3 years (S.D. =4.7). The study was approved by the Atomic Energy Commission Ethic Committee and all subjects gave written informed consent.

Stimulus design

The same stimuli were used for comparison and multiplication. On each trial, a fixation point first appeared for 300 msec on the centre of a computer screen. Then the fixation point was erased and two arabic digits, subtending $0.44 \times 0.79°$, were flashed for 150 msec at an eccentricity of 0.84° left and right of fixation. Finally, the screen remained empty for 850 msec before the next trial. The inter-trial interval was therefore 1300 msec. The pairs of digits were selected randomly by the computer on each trial from the digits 1–9, excluding pairs with two equal digits. The experiment was controlled by a portable PC-compatible T5100 Toshiba computer, with software-based msec timing routines and with stimulus presentation synchronized to the refresh cycle of an external raster display. Subjects viewed the display, which was placed 120 cm behind their head, via a small mirror placed 10 cm above their eyes. Accordingly, the digits were mirror-reversed on the screen so that they appeared normal to the subjects.

Instructions

The control condition consisted in resting silently with eyes closed with no particular instructions except to relax. For the number comparison condition, the subjects were instructed to maintain fixation while looking at the digit pairs, determine which of the two digits was the largest, and name it 'in their head'. For the multiplication condition, they were instructed to maintain fixation, multiply the two digits mentally and again name the result 'in their head'. In both cases, they were told to remain silent and to keep their mouth and lips perfectly still. This procedure was used to limit movement and brain activations related to overt speech which might have masked task-related activations. Before each condition, the subjects were given training both while naming the result aloud and while refraining from speaking. Just before the first multiplication block, a short questionnaire was also used to verify that the subjects had an adequate knowledge of multiplication facts.

Scanning procedure

Using positron emission tomography (PET) and oxygen-15-labelled water, normalized regional cerebral blood flow (NrCBF) was measured six times, the three conditions of rest control, number comparison and number multiplication being replicated twice. Condition order was the same for all subjects: two controls, two comparisons and two multiplications. (This was adopted after pilot studies suggested that subjects who took multiplication first experienced difficulties refraining from practising multiplication on subsequent resting and comparison blocks.) Stimulus presentation started 45 sec before water injection. For each condition, seven contiguous brain slices were acquired simultaneously on a time-of-flight PET system (TTV03-LETI, Grenoble, France; [39]). Following intravenous bolus injection of oxygen-15-labelled water [29], a single 80 sec scan was reconstructed (including correction for head attenuation) starting at the arrival of the radioactivity in the brain, the scan duration being chosen to improve the signal-to-noise ratio in the difference images [32]. The between-scan interval was 15 min. A series of 3 mm thick T1-weighted high resolution images of brain anatomy images were obtained in each subject at the same axial brain levels as his PET slices, using a 0.5 T magnetic resonance imager (MRMAX, General Electric, U.S.A.). These images were checked for absence of abnormalities in brain anatomy.

Data analysis

The data analysis method has been described and validated elsewhere [38]. It is aimed at detecting increases of cerebral blood flow in cerebral structures with known anatomical boundaries, based on a parcellation of the brain into regions of interest (see also [45]). In a first step, a detailed analysis of each subject brain anatomy was performed by means of a dedicated software (Voxtool, General Electric, Buc, France). The MRI slices were used to reconstruct a three-dimensional brain volume that was segmented further and allowed the display of the external and internal surfaces of both hemispheres together with three orthogonal views obtained by re-slicing the three-dimensional brain volume. The major gyri could then be identified and their limits automatically marked onto the MRI axial slices. Using these anatomical landmarks, cortical regions of interest (ROI) with anatomical boundaries, corresponding to the intersection of the gyri with the MRI axial slices, were delineated on each subject's MRI images. Subcortical regions were delineated directly on MRI images. This method does not require normalization to a fixed brain atlas, and takes into account inter-individual anatomical differences [20, 49] as well as hemispheric anatomical asymmetries [24, 26, 50]. It also makes the ROI boundaries independent of the CBF PET images and provides regional activation values for each individual (see Fig. 1). In order to compute regional normalized regional cerebral blood flow values (NrCBF), the seven PET slices acquired on each trial were aligned with the subject MRI by visually aligning three sets of isodensity contours automatically drawn on corresponding attenuation, blood flow and MRI slices. Within each anatomical ROI, NrCBF was estimated as the ratio (in per cent) of the radioactivity concentration in the region to that of the whole brain as measured in the PET images.

Statistical analysis

The NrCBF within each anatomical region was compared across the three experimental conditions and between hom-

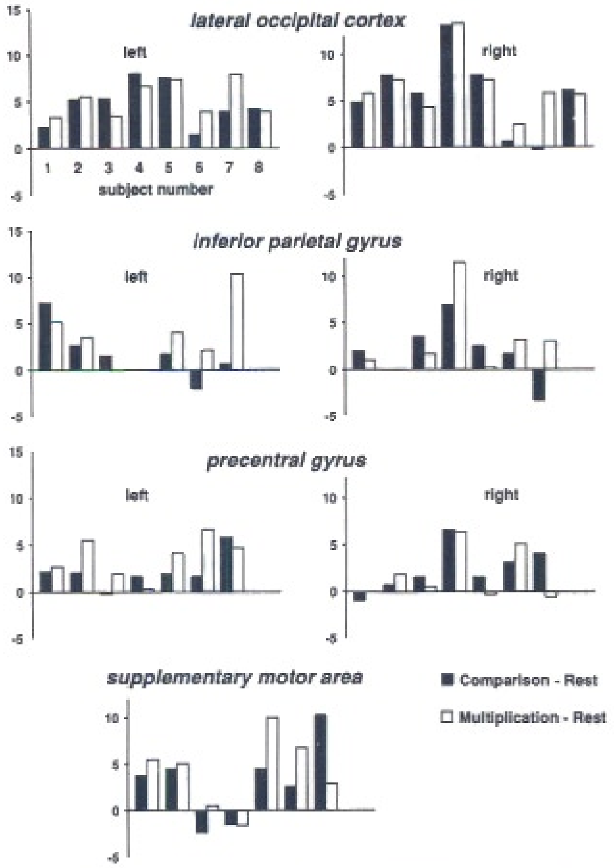

Fig. 1. Histograms showing the individual NrCBF variations (%) in selected regions of interest for comparison relative to rest and for multiplication relative to rest.

ologous regions in the left and right hemispheres. Regional data were analysed using a repeated measures ANOVA ($N = 16$) with factors of task (rest, multiplication, comparison) as well as hemisphere (left vs right) when appropriate. Pairwise contrasts were used to assess differences between rest and each experimental condition, as well as between the two experimental conditions. Effects were reported as significant whenever the two-tailed P-value was less than 0.05. Because of the exploratory nature of this study, no particular control of the overall type I error was applied.

Results

Table 1 shows the average NrCBF values in each of the three conditions and the P-values associated with the corresponding F-test. Histograms showing the individual variations in NrCBF appear in Fig. 1.

Significant differences between conditions indicating blood flow increases during multiplication, comparison, or both, were found in the right cuneus, the left and right lateral occipital cortices, the left and right precentral gyri, the supplementary motor area, and the left inferior parietal gyrus. Significant deactivations (blood flow decreases) during either task also occurred in the right precuneus, the left temporal pole, the left postcentral gyrus, the left and right supramarginal gyri, the left and right inferior frontal gyri, the left and right medial prefrontal regions, the right superior frontal gyrus, the right posterior cingulate gyrus and the right thalamus. In two other areas, the superior temporal gyrus and the middle temporal gyrus, activations or deactivations were seen depending on the arithmetical task used.

In order to better understand the contribution of each region, each task was contrasted separately to the resting condition. The results for comparison vs rest appear in Table 2 and in Fig. 2. When subjects were comparing numbers, NrCBF increased significantly in the left and right lateral occipital regions, the left and right precentral gyri, and the supplementary motor area. The left inferior parietal activation also was close to significance ($P = 0.076$). Significant deactivations were observed in the left postcentral gyrus, the left supramarginal gyrus, the left and right inferior frontal gyri, the right Brodmann area 6, the right thalamus, and the left superior temporal gyrus. Only the latter region showed a significant shift in asymmetry from rest to the comparison task (higher NrCBF on the right relative to the left during comparison relative to rest).

The results for multiplication versus rest appear in Table 3 and in Fig. 3. During multiplication, activations were again observed in the left and right lateral occipital regions, the left precentral gyrus (the right precentral gyrus fell short of significance, $P = 0.08$) and the supplementary motor area. In addition, NrCBF increased significantly in the right cuneus, the left fusiform and lingual gyri and the left and right inferior parietal gyri. Significant deactivations were observed in a large set of regions (Table 3). There was increased asymmetry in favour of the left hemisphere (higher NrCBF on the left relative to the right during multiplication relative to rest) in the superior frontal gyrus, the inferior frontal gyrus, and Brodmann's area 6.

Finally, multiplication was contrasted directly with comparison (Table 4, Fig. 4). The NrCBF was significantly higher during number comparison than during multiplication in five regions: the right superior temporal gyrus, the left and right middle temporal gyri, the right superior frontal gyrus and the right inferior frontal gyrus. Conversely, the only regions showing significantly higher NrCBF during multiplication than during comparison were the left lenticular nucleus, the right Brodmann area 8, and the right calcarine cortex. Hemispheric asymmetries indicating a significantly greater activation on the left side during multiplication and on the right side during comparison were observed in the superior temporal gyrus, the superior frontal gyrus, the precentral gyrus, and the inferior frontal gyrus. The converse pattern (greater activation on the left side during comparison and on the right side during multiplication) was found only in the right calcarine cortex.

Discussion

We used PET to measure regional cerebral blood flow while subjects either multiplied or compared the same

Table 1. Significant results of an ANOVA on NrCBF values (average normalized number of counts) in the three conditions*

Region		Rest	Comparison	Multiplication	ANOVA *P*
			Activations		
Cuneus	Left	115.4	118.0	118.1	0.30
	Right	124.8	126.8	129.0	0.040
Lateral occipital cortex	Left	97.4	102.1	102.6	<0.0001
	Right	93.9	99.6	100.4	<0.0001
Precentral gyrus	Left	108.4	110.5	112.1	0.0008 ($N=14$)
	Right	106.5	108.9	108.4	0.035 ($N=14$)
SMA		118.0	121.2	122.2	0.012 ($N=14$)
Inferior parietal gyrus	Left	107.3	109.2	111.4	0.005 ($N=12$)
	Right	98.3	100.5	101.8	0.068 ($N=12$)
			Deactivations		
Precuneus	Left	120.3	118.3	118.4	0.101
	Right	121.9	121.6	119.7	0.046
Temporal pole	Left	98.2	94.8	93.7	0.015
	Right	98.5	96.2	95.5	0.21
Postcentral gyrus	Left	105.9	104.4	104.2	0.016
	Right	106.0	104.4	104.3	0.116
Supramarginal gyrus	Left	111.6	109.5	108.5	0.007
	Right	109.2	108.0	106.9	0.012
Inferior frontal gyrus	Left	115.9	113.7	114.3	0.039
	Right	114.7	113.0	111.5	<0.0001
Medial prefrontal cortex	Left	122.4	120.9	119.7	0.034
	Right	115.0	112.9	111.5	0.019
Superior frontal gyrus	Left	102.8	102.1	101.1	0.286
	Right	105.5	104.6	101.5	<0.0001
Posterior cingulate gyrus	Left	111.7	110.3	109.0	0.148
	Right	121.0	117.8	117.0	0.046
Thalamus	Left	118.4	118.5	118.8	0.93
	Right	119.5	116.9	117.8	0.023
			Mixed pattern		
Superior temporal gyrus	Left	110.6	108.7	108.2	0.0002
	Right	109.3	109.9	107.8	0.024
Middle temporal gyrus	Left	104.3	104.9	103.5	0.050
	Right	102.9	104.1	102.8	0.13

*Note: $N=16$ unless otherwise stated. The *P*-value is for the main effect of task as a three-level variable.

pairs of digits, relative to a resting situation. The design of our study was constrained by the sensitivity of the PET scanner, which allowed only two scans in each of three conditions for each subject. Given this constraint, our choice of resting, multiplication and comparison conditions aimed at providing a maximum amount of data on

Table 2. Areas with significant NrCBF variations (%) in the comparison task relative to rest (*P*-value for Student's paired *t*-test)

Region	Left	Right	Right–left
		Activations	
Lateral occipital cortex	4.7 (<0.0001)	5.7 (0.0003)	1.0 (0.26)
Precentral gyrus	2.1 (0.017)	2.4 (0.005)	0.3 (0.81)
SMA	3.2 (0.042)		
		Deactivations	
Postcentral gyrus	−1.5 (0.045)	−1.6 (0.066)	−0.1 (0.77)
Supramarginal gyrus	−2.1 (0.039)	−1.2 (0.20)	0.9 (0.33)
Inferior frontal gyrus	−2.2 (0.033)	−1.7 (0.013)	0.5 (0.66)
Brodman's area 6	−0.1 (0.88)	−1.2 (0.026)	−1.1 (0.11)
Thalamus	0.1 (0.96)	−2.6 (0.028)	−2.7 (0.10)
		Mixed pattern	
Superior temporal gyrus	−1.9 (0.005)	0.6 (0.48)	2.5 (0.011)

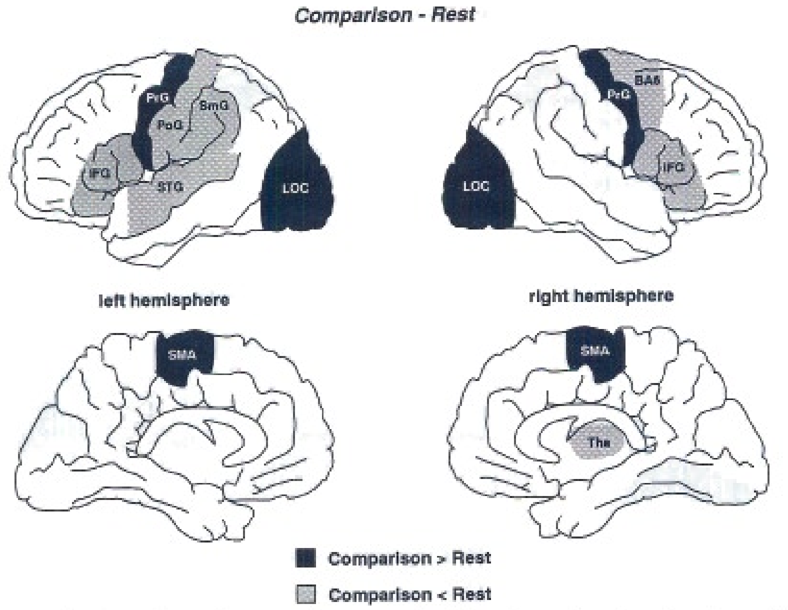

Fig. 2. Schematic representation of the regions of interest that were significantly activated or deactivated during comparison relative to rest, as projected on a lateral and mesial view of the two hemispheres. Abbreviations: LOC, lateral occipital cortex; PrG, precentral gyrus; SMA, supplementary motor area; PoG, postcentral gyrus; SmG, supramarginal gyrus; IFG, inferior frontal gyrus; BA6, Brodmann's area 6; Tha, thalamus; STG, superior temporal gyrus.

the cerebral networks involved in these two operations. Comparing brain activations during each arithmetical operation relative to rest, on the one hand, revealed a large set of task-related areas, most notably including the left and right inferior parietal areas during multiplication. Directly contrasting multiplication with comparison, on the other hand, revealed several areas that were differentially active in one operation relative to the other.

Obviously, such a design is open to several ambiguities in interpretation. First, since the control task was a rest task with eyes closed, we cannot distinguish, among the areas that were significantly activated during the active

Table 3. Areas with significant NrCBF variations (%) in the multiplication task relative to rest (P-value for Student's paired t-test)*

Region	Left	Right	Right–left
		Activations	
Cuneus	2.6 (0.13)	4.1 (0.024)	1.5 (0.42)
Lateral occipital cortex	5.2 (<0.0001)	6.4 (<0.0001)	1.2 (0.16)
Fusiform and lingual gyri	2.0 (0.050)	1.4 (0.36)	−0.5 (0.72)
Inferior parietal gyrus	4.1 (0.002)	3.4 (0.021)	−2.4 (0.13)
Precentral gyrus	3.7 (0.001)	1.9 (0.08)	−1.8 (0.13)
SMA	4.2 (0.008)		
		Deactivations	
Precuneus	−1.9 (0.057)	−2.2 (0.033)	−0.3 (0.80)
Superior temporal gyrus	−2.3 (0.0003)	−1.5 (0.078)	0.8 (0.32)
Temporal pole	−4.5 (0.019)	−3.0 (0.14)	1.5 (0.47)
Supramarginal gyrus	−3.0 (0.003)	−2.3 (0.002)	0.7 (0.50)
Postcentral gyrus	−1.7 (0.011)	−1.7 (0.12)	0.0 (0.88)
Superior frontal gyrus	−1.7 (0.095)	−4.0 (0.0004)	−2.3 (0.016)
Medial prefrontal cortex	−2.7 (0.022)	−3.5 (0.021)	−0.8 (0.62)
Inferior frontal gyrus	−1.6 (0.08)	−3.2 (<0.0001)	−1.6 (0.052)
Posterior cingulate gyrus	−2.7 (0.076)	−4.0 (0.016)	−1.3 (0.53)
Thalamus	0.4 (0.96)	−1.7 (0.047)	−2.1 (0.13)
		Mixed asymmetry pattern	
Brodmann's area 6	1.4 (0.24)	−1.2 (0.13)	−2.6 (0.04)

*Note: The inferior parietal gyrus was not sampled adequately in the left hemisphere of one subject and in the right hemisphere of another subject. As a result, for this region only, the column marked 'right–left' was computed with two data points less than the columns marked 'left' and 'right'.

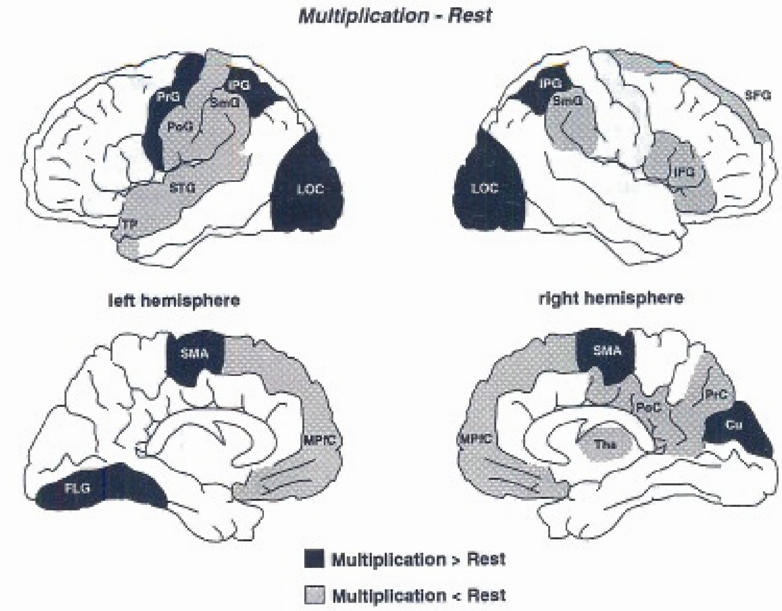

Fig. 3. Schematic representation of the regions of interest that were significantly activated or deactivated during multiplication relative to rest, as projected on a lateral and mesial view of the two hemispheres. Abbreviations: LOC, lateral occipital cortex; PrG, precentral gyrus; SMA, supplementary motor area; PoG, postcentral gyrus; SmG, supramarginal gyrus; IFG, inferior frontal gyrus; Tha, thalamus; STG, superior temporal gyrus; Cu, cuneus; FLG, fusiform and lingual gyri; IPG, inferior parietal gyrus; PrC, precuneus; TP, temporal pole; SFG, superior frontal gyrus; MPfC, medial prefrontal cortex; PoC, posterior cingulate gyrus.

tasks, those that are involved specifically in number processing and those that are related to non-numerical processes such as visual identification, attention orientation and response selection. This distinction must be made on the basis of other neuropsychological and brain-imaging findings. Thus, the strong activation of the left and right lateral occipital areas during both multiplication and comparison presumably reflected visual processing of the input digits, as did the small activation in the cuneus. Curiously, the right calcarine cortex was significantly more active during multiplication than during comparison (Table 4). Perhaps multiplication emphasized a left-to-right scanning of the input digits, thus yielding an attentional amplification [43] in right visual pathways. Activations in other areas probably were related to the output requirements of the tasks, which asked for the covert production of a verbal response. The supplementary motor area (SMA) and the precentral gyrus, which were non-specifically activated during both multiplication and comparison relative to rest, have been found active in several non-numerical paradigms including verbal production [42] and active visual fixation [44]. Hence, it is unlikely that they make a specific contribution to number processing.

Two reviewers of this article objected to the choice of a resting control and suggested using a control condition more directly comparable to the active tasks, for instance passive presentation or silent reading of arabic numerals. Obviously, had more scans been available, examining cerebral blood flow under such conditions would have been helpful. However, we decided against using such conditions as the main control for multiplication and

Table 4. Areas with significant NrCBF variations (%) in the multiplication task relative to the comparison task (*P*-value for Student's paired *t*-test)

Region	Left	Right	Right–left
	Multiplication > comparison		
Brodmann's area 8	1.6 (0.069)	1.4 (0.005)	−0.2 (0.82)
Lenticular nucleus	2.3 (0.011)	2.9 (0.090)	0.6 (0.76)
	Comparison > multiplication		
Superior temporal gyrus	−0.4 (0.32)	−2.1 (0.004)	−1.7 (0.038)
Middle temporal gyrus	−1.4 (0.050)	−1.3 (0.029)	0.1 (0.87)
Superior frontal gyrus	−1.0 (0.31)	−3.1 (0.0003)	−2.1 (0.010)
	Mixed pattern		
Calcarine cortex	−1.7 (0.15)	2.6 (0.034)	4.3 (0.032)
Precentral gyrus	1.5 (0.089)	−0.5 (0.59)	−2.0 (0.012)
Inferior frontal gyrus	0.57 (0.42)	−1.5 (0.020)	−2.0 (0.008)

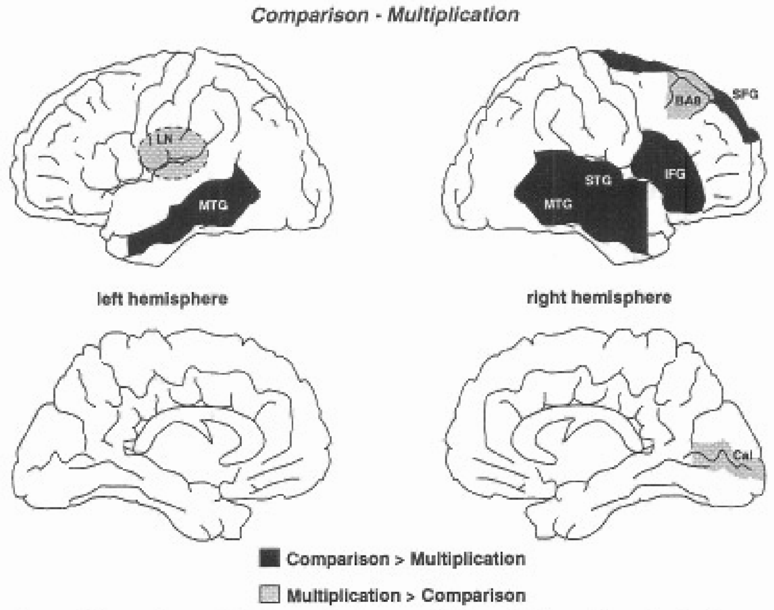

Fig. 4. Schematic representation of the regions of interest that were differentially activated during comparison and during multiplication, as projected on a lateral and mesial view of the two hemispheres. Abbreviations: BA8, Brodmann's area 8; STG, superior temporal gyrus; MTG, middle temporal gyrus; IFG, inferior frontal gyrus; SFG, superior frontal gyrus; Cal, calcarine cortex.

comparison tasks for fear that they would lead to an automatic activation of arithmetic memory and of quantity representations in the control state. Chronometric studies in normal subjects have provided considerable evidence that the mere presentation of a digit on screen is sufficient to evoke quantitative knowledge about this digit, even when the requested task is non-numerical in nature [12, 13, 17, 18, 27, 51, 52]. Likewise, flashing a pair of digits such as 2 and 4 may immediately and unconsciously activate their addition result, 6 [35, 36]. High-density recordings of event-related potentials suggest that left and right inferior parietal areas are active whenever numbers words are presented in a word categorization task [11]. Hence, presenting numbers in the control state might have had the undesirable effect of subtracting away activations in regions genuinely implicated in number processing. Generally speaking, the choice of an adequate control condition is a major problem for subtractive designs in brain imaging. In the present case, perhaps the passive presentation of pairs of meaningless geometrical symbols, accompanied by an internal stereotyped speech response, might have provided a more specific control better apt at isolating brain areas specialized for number processing.

Another related caveat of the present study is that the control 'resting' situation could involve uncontrolled brain activations which would have been subtracted from the set of regions involved in multiplication or in comparison. This may, perhaps, account for the numerous instances of 'deactivations' during experimental tasks relative to rest, as observed in the left and right supramarginal gyri, the left temporal pole, the left and right superior temporal gyri, the left and right inferior frontal gyri, and the right superior frontal gyrus. Such deactivations are frequent in PET experiments [see [19]] and may reflect internal speech during the 'resting' state, or the reorientation of attention away from the auditory modality during complex visual tasks [19, 43].

A third caveat is that the direct contrast between multiplication and comparison could not distinguish between areas that were active during one operation and areas that were deactivated during the other. Hence, interpretation of this direct contrast should be made with caution, and with due attention to the data from the rest condition. In particular, we believe that the right-lateralized set of areas that were significantly more active during comparison than during multiplication (superior and middle temporal gyri, superior and inferior frontal gyri) were actually deactivated during multiplication rather activated during comparison. Indeed, none of them were found active during comparison relative to rest. The multiplication task thus appeared to yield widespread and mostly right-lateralized frontal and temporal deactivations.

Finally, the reader should bear in mind that our statistical analysis was exploratory and used a statistical threshold uncorrected for multiple comparisons. Hence, our study should be viewed mostly as generating hypotheses for further research.

With these caveats in mind, several results of our study still appear noteworthy and should be pursued in future investigations. First, it is remarkable that the number comparison task did not yield any significant activations over and above those that we think are related to stimulus identification and response selection (lateral occipital cortex, precentral gyrus and SMA).

Hence, no critical brain areas for number comparison emerged from our study. We did, however, observe small activations (2%) in the left and right inferior parietal regions during comparison relative to rest (Table 1).

These activations did not differ significantly from those found during multiplication, although they were not strong enough to reach significance relative to rest ($P=0.078$ on the left). Their small magnitude may perhaps be related to the fact that the comparison task was noticeably easier than the multiplication task. High-density recordings of event-related potentials during number comparison have also revealed a bilateral parietal activation that is affected by numerical magnitude, does not vary with number notation, and emerges about 200 msec following the visual presentation of a target number [10].

Hence, a plausible working hypothesis is that number comparison relies on a magnitude representation redundantly represented in the left and right inferior parietal areas [15]. Studies of commissurotomized patients indeed suggest than both the right and the left hemisphere, in isolation, can identify and compare arabic numerals [21, 22, 47]. Although such studies must be interpreted with great care, because commissurotomy may not be complete and because of the possible effects of early brain reorganization in these patients, they do provide a putative explanation for why number comparison is not abolished by a unilateral left parietal lesion [6, 7, 14, 53], or even by an almost complete left hemispherectomy [25]. According to our hypothesis, only a bilateral parietal lesion could yield a permanent impairment of number comparison.

The present results also provide a sharper picture of the cerebral network involved in simple multiplications. Most notably, they confirm the strong involvement of the left and right inferior parietal gyri in this task. The implication of the left inferior parietal lobule in simple calculation is well documented in neuropsychology [3, 4, 23, 28, 53]. Our work reveals that the homologous region of the right hemisphere is also active, a result congruent with previous studies using functional methods such as the ^{133}Xe technique [46] or functional MRI [2]. The right inferior parietal area obviously takes part in calculation in normal subjects, even though it does not belong to the critical region whose lesioning causes acalculia.

Our data are relevant to the disputed issue of the localization of this critical region [4]. The present activations were restricted to the inferior parietal gyrus, which was defined as the part of the inferior parietal lobule located between the supramarginal gyrus, the angular gyrus, and the intraparietal sulcus (Fig. 3). No activation was found in the left and right angular gyri ($P>0.19$). The fact that previous studies have reported left and right angular gyrus activations in number processing [2, 46] may be related to the procedures used for anatomical referencing, the spatial resolution of the techniques, as well as the particular tasks that were selected.

As noted above, the function of the left and right inferior parietal areas might be to represent numbers in an abstract internal quantity or magnitude code. Why such a code is activated during multiplication is susceptible of different interpretations within models of number processing. One possibility is that the abstract amodal representation of numerical quantities must be accessed whenever numbers are processed mentally, be it for multiplication or comparison [40, 41]. Another possibility is that, although multiplication involves retrieval from rote verbal memory, encoding numbers as magnitudes is needed for re-coding the problem when direct retrieval fails [15]. For instance, an unfamiliar problem such as 9×2 can be re-coded as 2×9 (using the knowledge that 2 is smaller than 9), or as $20-2$ (using the fact that 9 is close to 10). Normal subjects use such semantic elaboration strategies most often for problems with large operands [34]. Hence, an interesting prediction is that the inferior parietal activation, if it is related to semantic elaboration, should increase with problem difficulty as indexed by the size of the operands. While this has not yet been tested with PET, high density recordings of event-related potentials while subjects multiply pairs of digits have revealed a left inferior parietal difference between problems with small operands and those with large operands, starting about 300 msec after the presentation of the second operand [33].

In addition to the inferior parietal area, two other brain areas, the left fusiform/lingual region and the left lenticular nucleus, may participate in the cerebral network underlying multiplication. The left fusiform/lingual region showed a small activation during multiplication vs rest. Patients with lesions of the left ventromesial occipito-temporal area often suffer from pure alexia and from difficulties in identifying digits, especially multi-digit numerals [16]. In two such patients, Cohen and Dehaene [7] have observed an inability to read aloud, add or multiply written arabic digits, with preservation of number comparison on written digits and of calculation on spoken operands. They proposed that the left fusiform/lingual region is specialized for identifying alphabetical or digital strings and transmitting them to areas involved in language production and in arithmetic fact retrieval.

The left lenticular nucleus was significantly active also during multiplication relative to comparison. In itself, this result appeared rather weak, because the activation was not significant when compared with rest. It may, however, be related to the growing number of published cases of acalculia following a lesion to the left basal ganglia [8, 30, 54]. In one well-studied case, Hittmair-Delazer *et al.* [30] demonstrated a severe deficit of arithmetical fact retrieval coupled with a surprising fluency at using semantic elaboration strategies to circumvent this deficit. For instance, the patient failed to retrieve 4×9 from memory, but could spontaneously and painfully compute it as $(90/2)-9$. Anatomically, the basal ganglia are involved in cortico-striato-pallido-thalamic loops that have been tentatively related to motor control and implicit memory [1, 31]. They may, therefore, provide an appropriate structure for the retrieval of rote verbal multiplication facts.

On the basis of such case studies and of the present PET results, a tentative framework for the cerebral network underlying the multiplication of two visually presented digits may be proposed [15]. The left infero-mesial occipito-temporal area would be involved in identifying the digits and in transmitting their identity to other left-hemispheric areas. The left basal ganglia would be involved in storing and retrieving rote verbal multiplication facts. Finally, the left and right inferior parietal areas would be called for whenever such direct retrieval fails, and would be involved in a semantic re-coding of the problem using quantitative knowledge of numbers. This framework, which is clearly very speculative, awaits further testing using finer-grained brain imaging paradigms.

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