

# Dissociating Prefrontal and Parietal Cortex Activation during Arithmetic Processing

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**Lesion and brain-imaging studies have implicated the prefrontal and parietal cortices in arithmetic processing, but do not exclude the possibility that these brain areas are also involved in nonarithmetic operations. In the present study, we used functional magnetic resonance imaging to explore which brain areas contribute uniquely to numeric computation. Task difficulty was manipulated in a factorial design by varying the number of operands and the rate of stimulus presentation. Both manipulations increased the number of operations to be performed in unit time. Manipulating the number of operands allowed us to investigate the specific effect of calculation, while manipulating the rate of presentation allowed us to increase task difficulty independent of calculation. We found quantitative changes in activation patterns in the prefrontal and parietal cortices as well as the recruitment of additional brain regions, including the caudate and midcerebellar cortex, with increasing task difficulty. More importantly, the main effect of arithmetic complexity was observed in the left and right angular gyrus, while the main effect of rate of stimulus presentation was observed in the left insular/orbitofrontal cortex. Our findings indicate a dissociation in prefrontal and parietal cortex function during arithmetic processing and further provide the first evidence for a specific role for the angular gyrus in arithmetic computation independent of other processing demands.** © 2000 Academic Press

**Key Words:** fMRI; arithmetic; parietal lobe; prefrontal cortex.

## INTRODUCTION

Mathematical reasoning is at the core of logical thought and consequently represents an important component of higher order cognition (Dehaene, 1993; Luria, 1966). Cognitive neuroanatomical models of arithmetic processing have, until recently, been largely based on human brain lesion studies. Although classically the parietal cortex is thought to underlie the acalculia component of Gerstmann's syndrome, acalculia

has also been reported in patients with lesions to both prefrontal cortex (Fasotti *et al.*, 1992; Luria, 1966) and parietal cortex (Benson and Weir, 1972; Henschen, 1920; McCarthy and Warrington, 1988; Takayama *et al.*, 1994; Warrington, 1982; Whalen, 1997) as well as subcortical structures including the thalamus (Ojemann, 1974). These lesions often have dramatic consequences for arithmetic processing; however, they appear to be variable in the specific type of arithmetic deficits that are seen in individual patients (Kahn and Whitaker, 1991; McCloskey *et al.*, 1991).

Imaging studies with normal subjects have identified a number of brain regions involved in performance of arithmetic tasks (Burbaud *et al.*, 1995; Dehaene *et al.*, 1999). For example, Dehaene *et al.* (1999) attempted to dissociate frontal linguistic processes involved in arithmetic calculation by examining differences between approximate and exact calculations, with the latter thought to involve more linguistic processing. They reported greater activation in bilateral inferior parietal lobule, right precuneus, bilateral precentral sulci, left dorsolateral prefrontal cortex, left superior prefrontal gyrus, left cerebellum, and left and right thalami during approximate computation. During exact computation, greater activation was reported in left inferior prefrontal, left cingulate gyrus, left precuneus, right parieto-occipital sulcus, left and right angular gyrus, and right middle temporal gyrus. Despite considerable variability in regional patterns of activation observed, imaging studies do collectively suggest that both the prefrontal and the parietal cortices are involved in arithmetic tasks. Although these findings have identified several key distinct brain areas involved in arithmetic processing, the reported data do not exclude the possibility that some or all of these brain areas are involved in nonarithmetic operations. Indeed, considerable overlap exists between the brain regions that have been implicated and those involved in, for example, attention, working memory, and lexical and linguistic processes. Thus, little progress has been made in demarcating the brain areas that contribute uniquely to numeric computation.

In this study, we investigate how brain activation changes as the amount of computation is manipulated, an issue that has been left unexplored by studies to date. This paradigm provides us with a mechanism for discerning which brain areas are critically involved in arithmetic operations. Previous imaging studies of arithmetic processing have been limited to reporting brain activation during either addition (Dehaene *et al.*, 1999) or subtraction (Burbaud *et al.*, 1995, 1999; Rueckert *et al.*, 1996). We use addition and subtraction as basic arithmetic operations in order to reduce the amount of arithmetic fact retrieval and rote memory. Subjects viewed arithmetic equations in the form " $a + c - b = d$ " and were asked to judge whether the results were correct. The difficulty of arithmetic operations was manipulated in a factorial design using two levels of arithmetic complexity (two or three operands) and two levels of stimulus presentation rate. Both manipulations increased the number of operations to be performed in unit time. The three-operand condition involved both an additional operand and switching between addition and subtraction. Manipulating the number of operands therefore allowed us to investigate the general effect of arithmetic complexity. On the other hand, manipulating the rate of presentation allowed us to increase task difficulty independent of calculation.

We investigate which brain regions show changes in activation across these experimental factors. Regional changes in activation across levels of these factors would reveal which brain regions are most critical for performing the arithmetic task and which regions provide supporting functions. We hypothesized that processing rate and number of operands would differentially affect the prefrontal and parietal cortices.

## MATERIALS AND METHODS

### Subjects

Sixteen healthy, right-handed subjects (8 males and 8 females; ages 16.84–23.02 years mean 20.28) participated in the study after giving written informed consent. The Human Subjects Committee at Stanford University School of Medicine approved all protocols used in this study. Subjects were also assessed using the Wechsler Adult Intelligence Scale, 3rd ed. (WAIS-III).

### Six-Second Math Experimental Design

The experiment began with a 30-s rest epoch followed by six alternating 30-s epochs of "easy" (two-operand equation) experimental trials and control trials. These six easy experimental epochs were followed by a second 30-s rest epoch. Following the second rest were six alternating 30-s epochs of "difficult" (three-operand equation) experimental trials and control tri-

als. Following these six difficult experimental epochs was a third 30-s rest epoch. During the rest condition, subjects passively viewed a blank screen. Easy experimental epochs consisted of five two-operand addition or subtraction problems (randomly intermixed) with either a correct or an incorrect resultant (e.g.,  $1 + 2 = 3$  or  $5 - 2 = 4$ ). Difficult experimental epochs consisted of five three-operand addition/subtraction problems with either a correct or an incorrect resultant (e.g.,  $6 - 3 + 5 = 8$  or  $6 + 2 - 3 = 4$ ). All experimental and control stimuli were presented for 5250 ms, with an ISI of 750 ms. Sixty percent of the results were correct and required a button press and the other 40% were incorrect. Equal numbers of button presses were required for experimental and control trials. Of the incorrect-resultant trials, half of the results were one more than the correct answer, and half were one less than the correct answer. During all experimental epochs the instruction "Push if Correct" was displayed for the entire length of the epoch. Subjects were instructed to respond with a key press only when the resultant of the math equation was correct. Control epochs for the blocks of easy experimental trials comprised five stimuli, each consisting of a string of five single digits. Control epochs for the blocks of difficult experimental trials comprised five stimuli, each consisting of a string of seven single digits. During the control epochs the instruction "Push for 0" was displayed the entire length of the epoch (6000 ms). Subjects were instructed to respond with a key press only when a 0 appeared in the string of digits.

### Three-Second Math Experimental Design

The design of the 3-s math experiment was identical to that of the 6-s experiment with three exceptions. First, the easy and difficult experimental and control epochs consisted of nine, rather than five stimuli. Second, each stimulus was presented for 2625 ms (rather than for 5250 ms), with an ISI of 708 ms (rather than 750 ms). Third, 66% of the results were correct and required a button press (as opposed to 60%) and the remaining 34% were incorrect.

### Behavioral Data Analysis

The reaction time (RT) and number of correct and incorrect responses to Experimental and Control events were computed separately for the 6-s and the 3-s math experiments. Percentage correct and incorrect responses and RTs were compared using an analysis of variance (ANOVA).

### fMRI Acquisition

Images were acquired on a 1.5-T GE Signa scanner with Echospeed gradients using a custom-built whole-head coil that provides a 50% advantage in signal-to-

noise ratio over that of the standard GE coil (Hayes and Mathias, 1996). A custom-built head holder was used to prevent head movement. Eighteen axial slices (6 mm thick, 1 mm skip) parallel to the anterior and posterior commissure covering the whole brain were imaged with a temporal resolution of 2 s using a T2\*-weighted gradient echo spiral pulse sequence (TR = 2000 ms, TE = 40 ms, flip angle 89°, and one interleave) (Glover and Lai, 1998). The field of view was 240 mm and the effective in-plane spatial resolution was 4.35 mm. To aid in localization of functional data, high-resolution T1-weighted spoiled grass gradient recalled 3D MRI sequence with the following parameters was used: TR = 24 ms, TE = 5 ms, flip angle 40°, 24-cm field of view, 124 slices in sagittal plane, 256 × 192 matrix, acquired resolution 1.5 × 0.9 × 1.2 mm. The images were reconstructed as a 124 × 256 × 256 matrix with a 1.5 × 0.9 × 0.9-mm spatial resolution. Structural and functional images were acquired in the same scan session.

The task was programmed using Psyscope (Cohen *et al.*, 1993) on a Macintosh (Sunnyvale, CA) notebook computer. Initiation of scan and task was synchronized using a TTL pulse delivered to the scanner timing microprocessor board from a CMU Button Box microprocessor (<http://poppy.psy.cmu.edu/psyscope>) connected to the Macintosh. Stimuli were presented visually at the center of a screen using a custom-built magnet-compatible projection system (Resonance Technology, CA).

### Image Preprocessing

Images were reconstructed, by inverse Fourier transform, for each of the 225 time points into 64 × 64 × 18 image matrices (voxel size 3.75 × 3.75 × 7 mm). fMRI data were preprocessed using SPM99 (<http://www.fil.ion.ucl.ac.uk/spm>). Images were corrected for movement using least-square minimization without higher order corrections for spin history and normalized to stereotaxic Talairach coordinates (Talairach and Tournoux, 1988). Images were then resampled every 2 mm using sinc interpolation and smoothed with a 4-mm Gaussian kernel to decrease spatial noise.

### Statistical Analysis

Statistical analysis was performed on individual and group data using the general linear model and the theory of Gaussian random fields as implemented in SPM99 (Friston *et al.*, 1995). This method takes advantage of multivariate regression analysis and corrects for temporal and spatial autocorrelations in the fMRI data. Activation foci were superposed on high-resolution T1-weighted images and their locations inter-

preted using known neuroanatomical landmarks (Duvvernoy and Bourgouin, 1999; Mai *et al.*, 1997).

A within-subjects procedure was used to model all the effects of interest for each subject. Individual subject models were identical across subjects (i.e., a balanced design was used). Confounding effects of fluctuations in global mean were removed by proportional scaling in which, for each time point, each voxel was scaled by the global mean at that time point. Low-frequency noise was removed with a high-pass filter (0.5 cycles/min) applied to the fMRI time series at each voxel. A temporal smoothing function (Gaussian kernel corresponding to dispersion of 8 s) was applied to the fMRI time series to enhance the temporal signal-to-noise ratio. We then defined the effects of interest for each subject with the relevant contrasts of the parameter estimates.

Group analysis was performed using a random-effects model that incorporated a two-stage hierarchical procedure. This model estimates the error variance for each condition of interest across subjects, rather than across scans (Holmes and Friston, 1998), and therefore provides a stronger generalization to the population from which data are acquired. This analysis proceeded in two steps. In the first step, contrast images for each subject and each effect of interest were generated as described above. In the second step, these contrast images were analyzed using a general linear model to determine voxel-wise *t* statistics. One contrast image was generated per subject, per effect of interest (e.g., 3-s ISI, two-operand condition, minus the control condition). A one-way *t* test was then used to determine group activation for each effect. Finally, the *t* statistics were normalized to *Z* scores, and significant clusters of activation were determined using the joint expected probability distribution of height and extent of *Z* scores (Poline *et al.*, 1997), with height ( $Z > 2.33$ ;  $P < 0.01$ ) and extent thresholds ( $P < 0.01$ ).

Contrast images were calculated using a within-subject design for the following conditions: (i) 3-s ISI, three operand; (ii) 3-s ISI, two operand; (iii) 6-s ISI, three operand; (iv) 6-s ISI, two operand; (v) main effect of rate; (vi) main effect of number of operands; and (vii) interaction between rate and number of operands. In order to calculate the main effect of number of operands, activation was averaged across the two levels of ISI, and the two-operand activation was subtracted from the three-operand activation. The main effect of rate (ISI) was calculated by averaging activation across the two levels of number of operands and subtracting 6-s ISI activation from 3-s ISI activation. Taking “3-operand minus 2-operand” activation for the 3-s ISI and subtracting “3-operand minus 2-operand” activation for the 6-s ISI determined the interaction effect.

TABLE 1

Behavioral Data: Mean Percentage Correct, Reaction Times, and False Alarms for Experimental and Control Conditions

	6-s ISI, control equations	6-s ISI, 2-operand equations	6-s ISI, 3-operand equations	3-s ISI, control equations	3-s ISI, 2-operand equations	3-s ISI, 3-operand equations
Mean % correct (SD)	99.6 (0.011)	98.7 (0.027)	96.7 (0.059)	99.5 (0.008)	97.9 (0.027)	95.8 (0.060)
Mean RT (SD)	818.44 (144.03)	1233.87 (224.85)	2012.34 (327.29)	733.52 (107.98)	960.04 (198.47)	1696.43 (343.34)
Mean % false alarms (SD)	0.2 (0.008)	1.3 (0.027)	2.5 (0.041)	0	1.6 (0.019)	1.2 (0.018)

## RESULTS

### Neuropsychological Assessments

The mean ( $M$ ) and standard deviations (SDs) for the WAIS-III scores were as follows: full-scale IQ,  $M = 130$ ,  $SD = 8.65$ ; verbal IQ,  $M = 130.25$ ,  $SD = 8.87$ ; performance IQ,  $M = 123.06$ ,  $SD = 9.65$ ; the arithmetic subscale,  $M = 14.25$ ,  $SD = 2.57$ ; working-memory index,  $M = 117.2$ ,  $SD = 13.95$ ; and processing-speed index,  $M = 120$ ,  $SD = 12.88$ . Regression correlation analyses showed no significant relationship between behavioral performance on the tasks and any of these IQ measures.

### Behavioral

Mean percentage correct, RTs, and false alarms for the four experimental conditions are shown in Table 1. Each dependent variable was analyzed using a  $2 \times 3$  repeated-measures ANOVA with within-subjects variables of ISI (3-s vs 6-s) and trial type (three-operand equations, two-operand equations, or control trials).

The analysis of percentage correct revealed a significant main effect of trial type,  $F(2, 30) = 5.645$ ,  $P < 0.01$ . The main effect of trial type indicates that percentage correct is lowest for the three-operand equation trials and highest in the control trials (see Table 1). Neither the main effect of ISI nor the interaction was significant.

The analysis of reaction times revealed significant main effects of ISI,  $F(1, 15) = 65.03$ ,  $P < 0.000$ , and trial type,  $F(2, 30) = 170.25$ ,  $P < 0.000$ . In addition, there emerged a significant interaction between ISI and trial type,  $F(2, 30) = 9.76$ ,  $P < 0.000$ . Post hoc Sheffe tests showed that reaction time was higher for the 6-s compared to the 3-s presentation in the two-operand ( $P < 0.000$ ) and the three-operand conditions ( $P < 0.000$ ), whereas in the control trials, reaction time was equivalent for the two ISIs ( $P > 0.47$ ). Note that reaction times were consistently longer for the 6-s ISI equations, even though these were presumably less difficult than the 3-s ISI equations. We attribute this difference to the fact that subjects had a longer time in which to respond per trial.

The analysis of false alarms revealed no significant main effects or interactions.

### Brain Activation

All activations reported below are for experimental conditions contrasted with the corresponding control conditions. No significant clusters of activation were observed for the 6-s ISI, two-operand condition. For the 6-s, three-operand condition, significant activation was observed in the right inferior frontal gyrus (IFG), left IFG and middle frontal gyrus (MFG), left supramarginal gyrus (SMG), left angular gyrus (ANG), right ANG, and left presupplementary motor area (pre-SMA). For the 3-s ISI, two-operand condition, significant activation was observed in the left and right IFG, left MFG, left SMG, left ANG, left inferior temporal gyrus (ITG), left pre-SMA, and left premotor cortex. Finally, the largest amount of activation was observed in the 3-s ISI, three-operand condition. In addition to the bilateral IFG, MFG, ANG, SMG, premotor cortex, left pre-SMA, and left ITG, significant activation was observed in the left and right middle cerebellum, left and right caudate, and left ventrolateral nucleus of the thalamus. Table 2 provides further details concerning the regions activated in each of these conditions. Figure 1 shows the surface rendering for the three conditions where significant clusters of activation were found.

### Main Effect of Rate

A significant main effect of rate of stimulus presentation was observed in the left insula and the basal operculum of the orbitofrontal gyrus. Table 2 shows the details of the activation focus, Fig. 2a shows a surface rendering of the activation, and Fig. 3a provides a more precise localization of the activation superposed on a high-resolution structural image. Figure 4 (top row) depicts the activation time series from a 3-mm<sup>3</sup> region surrounding the peak activation for the main effect of rate and shows greater activation during the 3-s compared to the 6-s stimulus presentation.

TABLE 2

Brain Areas That Showed Significantly Greater Activation during the Four Experimental Conditions Involving Arithmetic Processing, Compared to the Control Conditions

Comparison	Area	<i>P</i> value	No. of voxels in cluster	<i>Z</i> max	Peak coordinates		
3-s 3-operand	R ANG/intraparietal sulcus (BA 39/7)	0.000	2381	5.61	30	-76	40
	L ANG/intraparietal sulcus (BA 39/7)	0.000	6619	5.37	-26	-78	42
	<i>L SMG/ANG (BA 40)</i>			<i>9.46</i>	<i>-48</i>	<i>-50</i>	<i>50</i>
	<i>L ITG (BA 37)</i>			<i>6.15</i>	<i>-50</i>	<i>-62</i>	<i>-10</i>
	<i>L middle cerebellum</i>			<i>3.88</i>	<i>-36</i>	<i>-66</i>	<i>-36</i>
	Pre-SMA/premotor (BA 6)	0.000	4902	5.29	0	16	58
	<i>L IFG/MFG (BA 44/9)</i>			<i>5.67</i>	<i>-44</i>	<i>10</i>	<i>26</i>
	<i>L orbital gyrus/frontal operculum</i>			<i>4.15</i>	<i>-42</i>	<i>26</i>	<i>-4</i>
	<i>L premotor (BA 44/45)</i>			<i>4.58</i>	<i>-36</i>	<i>-2</i>	<i>44</i>
	R IFG/MFG (BA 44/45)	0.000	2533	4.35	52	12	22
	<i>R orbital gyrus/frontal operculum</i>			<i>4.13</i>	<i>32</i>	<i>26</i>	<i>2</i>
	R middle cerebellum	0.000	740	4.32	36	-62	-42
	R premotor/MFG (BA 6)	0.020	356	4.28	28	4	64
	L caudate	0.000	1305	4.15	-16	-4	6
<i>L thalamus (VL)</i>			<i>4.13</i>	<i>-12</i>	<i>-14</i>	<i>8</i>	
<i>R caudate</i>			<i>3.82</i>	<i>8</i>	<i>6</i>	<i>4</i>	
3-s, 2-operand	R IFG (BA 44/45)	0.000	1235	4.77	54	32	16
	L SMG/ANG (BA 39/40)	0.001	582	4.53	-44	-48	8
	L pre-SMA (BA 6)	0.004	501	4.42	-6	12	50
	L ITG (BA 37)	0.044	326	4.13	-52	-50	-14
	Premotor (BA 6)	0.000	974	3.77	-30	-4	60
	<i>L IFG/MFG (BA 44/45)</i>			<i>3.44</i>	<i>-42</i>	<i>28</i>	<i>26</i>
6-s, 3-operand	L SMG/ANG (BA 40)	0.000	2247	4.66	-48	-50	48
	R IFG (BA 44)	0.029	317	4.59	50	14	24
	R angular gyrus (BA 39/19)	0.000	1606	4.35	30	-76	30
	L IFG op/MFG (BA 44/9)	0.000	1003	4.17	-52	10	30
	L pre-SMA (BA 6)	0.005	426	3.80	-2	22	44
6-s, 2-operand	<i>No suprathreshold clusters</i>						
Main effect, rate	L insular/orbital gyrus	0.002	395	3.48	-34	16	-8
Main effect, operands	R ANG/intraparietal sulcus (BA 39/7)	0.000	823	4.16	26	-70	48
	L ANG/intraparietal sulcus (BA 39/7)	0.035	273	3.30	-26	-82	38
	L pre-SMA	0.011	334	3.95	-12	14	54
Interaction—rate and number of operands	<i>No suprathreshold clusters</i>						

Note. For each significant cluster, the region of activation, cluster-level significance level, number of voxels activated, maximum *Z* score, and location of peak are shown. Secondary peaks are in italics.

### Main Effect of Operands

A significant main effect of number of operands was observed in the left and right angular gyrus and adjoining intraparietal sulcus as well as the left pre-SMA. Table 2 shows the details of the activation focus, Fig. 2b shows a surface rendering of the activation, and Fig. 3b provides a more precise localization of the activation superposed on a high-resolution structural image. Figure 4 (middle and bottom rows) depicts the activation time series from a 3-mm<sup>3</sup> region surrounding the peak activation for the main effect of operands in the left and right parietal cortex and shows greater activation during the three-operand, compared to the two-operand, condition.

### Interaction of Rate and Number of Operands

No significant interaction between rate and number of operands was observed in any brain region.

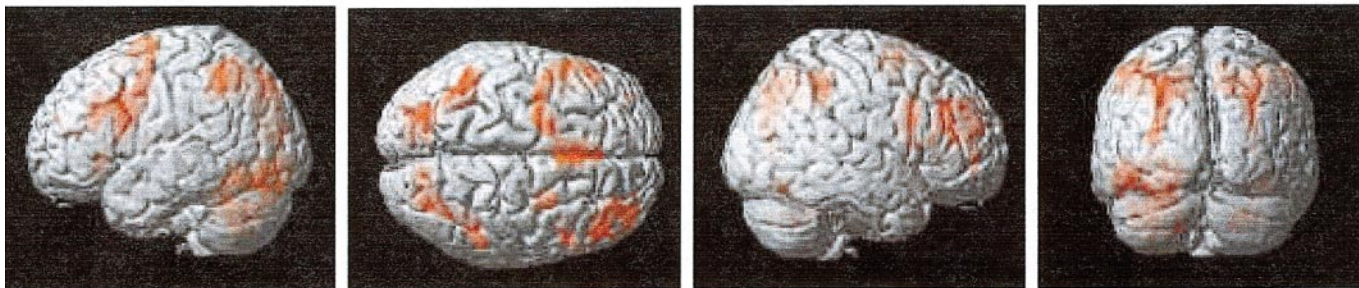
### Main Effect of Rate in the Control Condition

When the data for just the control conditions were analyzed, a main effect of rate emerged in the left insula/opercular cortex and in the right insula.

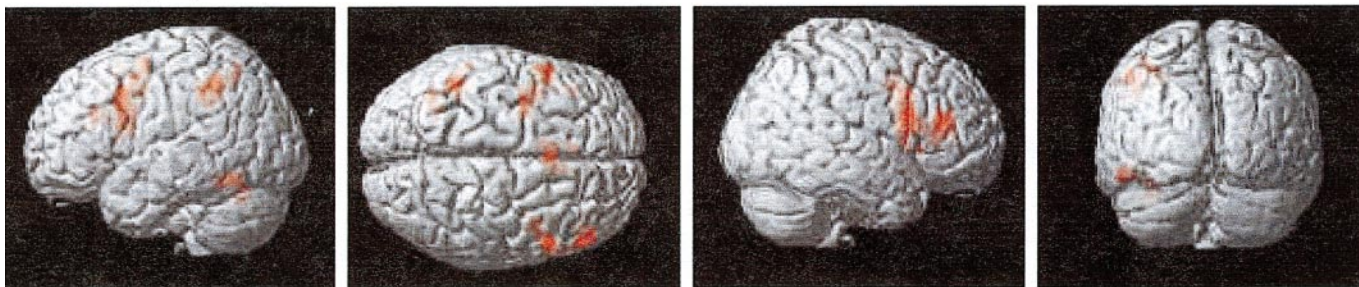
### Main Effect of Length of Digit String in the Control Condition

When the data for just the control conditions were analyzed, no main effects were observed in any brain region.

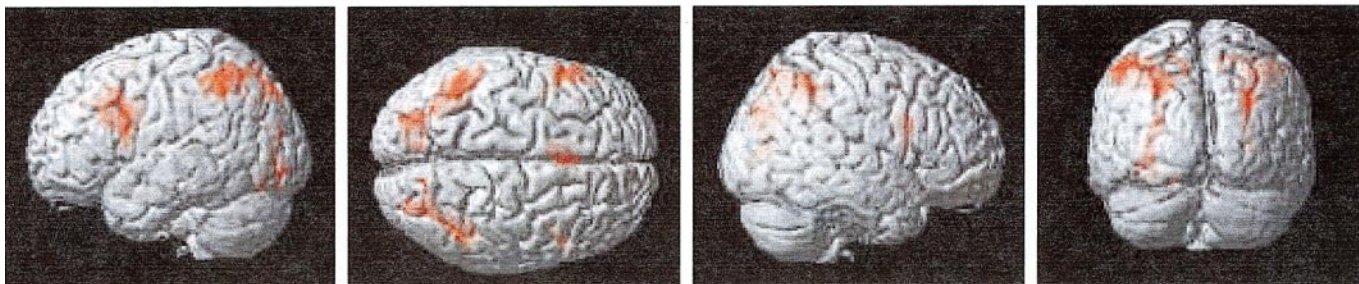
a 3-second, 3-operand



b 3-second, 2-operand



c 6-second, 3-operand

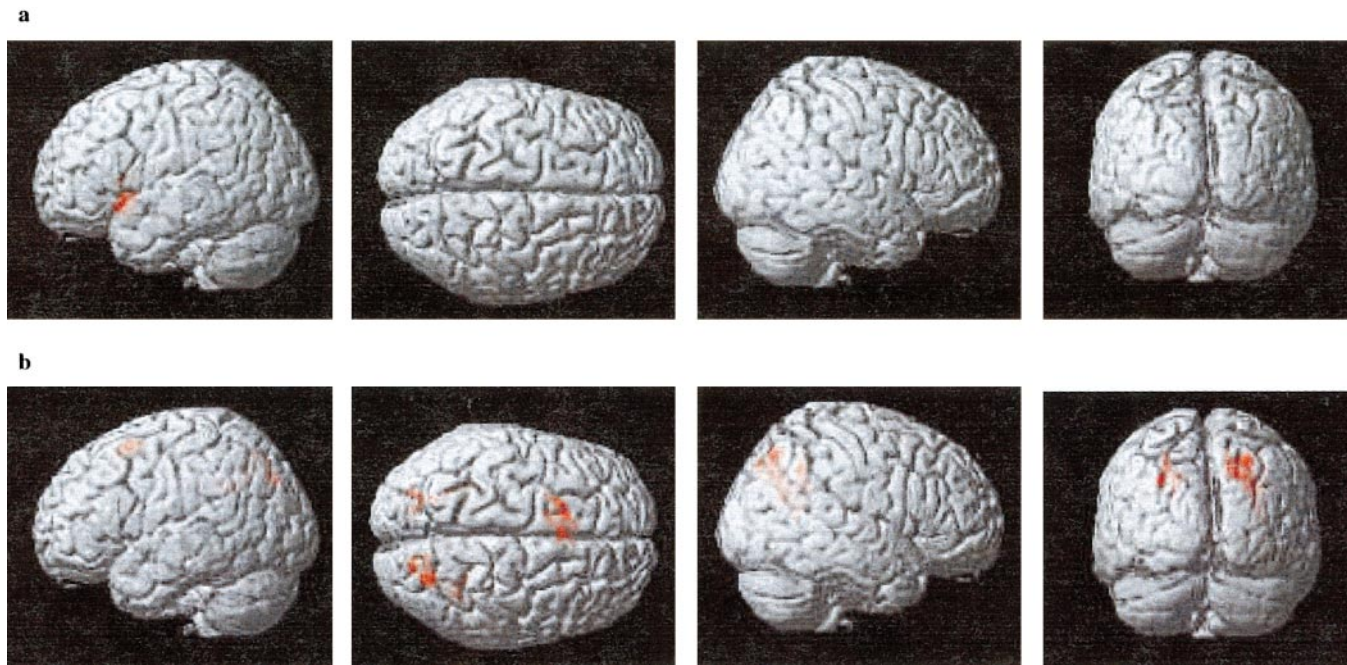


**FIG. 1.** Brain areas that showed significantly greater activation during three experimental conditions involving arithmetic processing, contrasted to the control conditions. Significant activation was observed in a number of regions in the inferior and middle frontal gyri as well as the angular and supramarginal gyri in the parietal cortices. All activations reported in the present study were significant after height ( $Z > 2.33$ ;  $P < 0.01$ ) and extent ( $P < 0.01$ ) thresholding.

## DISCUSSION

Consistent with previous imaging studies, we found activation related to arithmetic processing in the inferior and middle prefrontal gyri, the angular and supramarginal gyri, and a number of other discrete brain regions (Burbaud *et al.*, 1995). These regions also showed increased activation with overall task difficulty. Increases were observed both in the height and in the spatial extent of activation. Compared to the 3-s ISI, two-operand condition, the 3-s ISI, three-operand condition resulted in a more than twofold increase in the number of activated voxels in the prefrontal and parietal cortices. In addition, this most difficult condition resulted in the recruitment of the left and right caudate, left thalamus, and left and right middle cerebellum. These results suggest that additional cortico-thalamic–cerebellar circuits are recruited when more complex and rapid arithmetic processing is required.

The fact that the behavioral data revealed no interaction between number of operands and rate of stimulus presentation indicates that the two factors contribute independently to the task. This provides justification for assessing brain activation related to each factor separately. We observed significant changes with increase in rate of presentation only in the left frontal-insular region. This region borders, but appears to be distinct from, the opercular part of the inferior frontal gyrus. Previous imaging studies have found increased activation in the sensory cortex with increasing rate of presentation of auditory stimuli (Rees *et al.*, 1997); however, stimuli in the present study were presented at equal rates in both the arithmetic processing and the control conditions. Thus, the observed increase in activation with rate in the prefrontal cortex is not attributable to the requirement for rapid sensory processing. This region also showed an

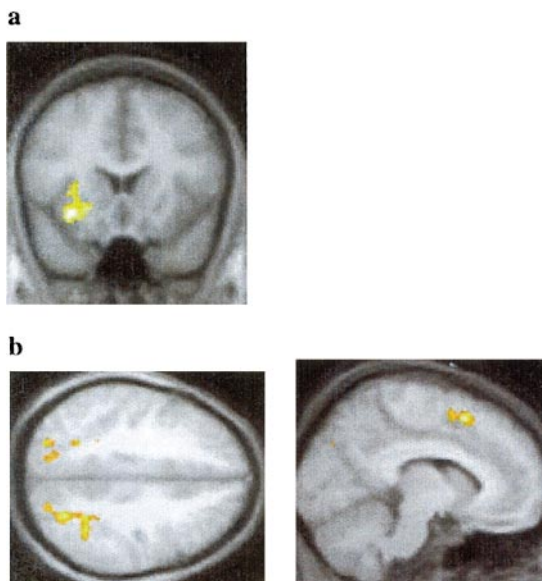


**FIG. 2.** The main effect of rate of stimulus presentation was observed in the prefrontal cortex (a) and the main effect of number of operands was observed in the parietal cortex (b).

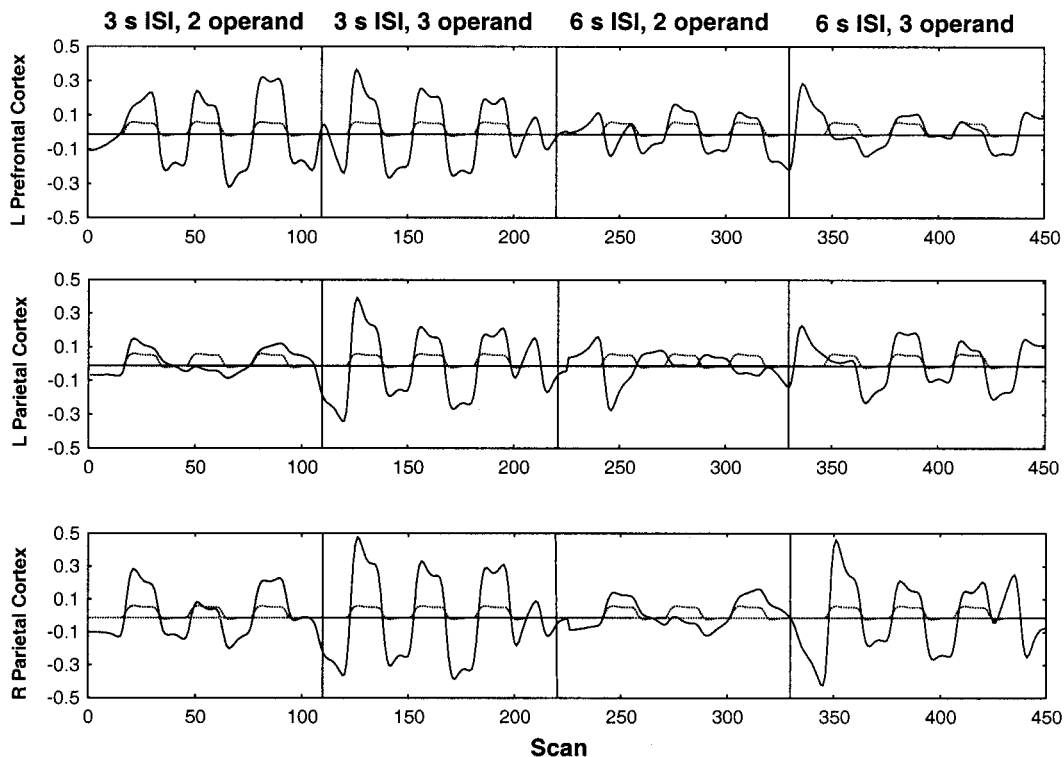
effect of rate in the control condition, suggesting that it may be more generally involved in rapid perceptual and cognitive processing of stimuli. Further, this re-

gion is modulated by task difficulty since greater activation was observed in the experimental than in the control condition. Further studies are needed to elucidate whether this result applies more generally to other complex cognitive tasks. The functional role of the orbitofrontal-insular cortex activated in the present study has not been extensively investigated in neurophysiological studies. However, Rolls (1998) has suggested the involvement of the orbitofrontal cortex in the rapid learning of visual associations. Future studies should explore whether the effects of rapid processing are present in the adjoining opercular part of the inferior frontal gyrus and whether rate-related activation in both regions may be task- or modality-specific.

With increasing number of operands, significant activation was observed bilaterally in a circumscribed region in the angular gyrus and adjoining intraparietal sulcus. No rate-related increase was observed in this region. Further, this region did not show an interaction between number of operands and rate. This pattern mirrors the lack of interaction found in our behavioral data and strengthens our suggestion of independence of the two factors. Therefore, the main effect of number of operands found in the parietal cortex appears to be task-specific and not to arise from generic task difficulty. Our findings provide the first evidence that brain activity in the angular gyrus and adjoining intraparietal sulcus is directly related to the degree of arithmetic complexity. These results are in excellent agreement with lesion studies (Benson and Weir, 1972;



**FIG. 3.** Precise localization of brain regions showing main effects of rate of stimulus presentation and number of operands. (a) The main effect of rate of stimulus presentation was observed in the basal opercular region of the orbitofrontal gyrus and the insular region adjoining the inferior frontal gyrus. (b) The main effect of number of operands was observed bilaterally in the angular gyrus and adjoining intraparietal sulcus in the parietal lobe (left) as well as the supplementary motor area (right). Activations are shown superposed on group-averaged ( $n = 16$ ) high-resolution structural images.



**FIG. 4.** Activation time series (solid black line) for each of the four factors (3-s ISI, 2 operands; 3-s ISI, 3 operands; 6-s ISI, 2 operands; 6-s ISI, 3 operands) are shown. These time series show the main effect of rate in the left inferior frontal cortex and the main effect of operand in the left and right parietal cortex. The expected response is shown as a dashed line.

Henschen, 1920; McCarthy and Warrington, 1988; Takayama *et al.*, 1994; Warrington, 1982; Whalen, 1997).

Significant activation related to number of operands was also observed in the left pre-SMA. This activation is anterior to the anterior commissure and may reflect preparation for motor output that accompanies multi-stage numerical computations during the three-operand condition. The three- and two-operand condition RTs differed by more than 850 ms. The increase in pre-SMA activation may reflect the longer duration of the motor preparatory activity in the three-operand, compared to the two-operand, condition. Electrophysiological recordings have consistently implicated the SMA and pre-SMA during motor preparation (Tanji and Mushiake, 1996). The pre-SMA activation in the present study appears to be related more to the state of preparedness to select a motor response than to motor preparation per se, as has been found during an fMRI study of delay-related activation during working memory (Petit *et al.*, 1998).

In our three-operand addition and subtraction problems, it is unlikely that subjects are simply retrieving addition and subtraction facts, since there is nearly an infinite combination of three-operand possibilities. In other words, they must *compute* the answer. Thus, our data provide the best evidence to date that very local-

ized regions of the parietal lobe are specifically involved in arithmetic computation. Because the angular gyrus is also activated by a number of other tasks, e.g., working memory (Smith and Jonides, 1997) and language (Crozier *et al.*, 1999; Jessen *et al.*, 1999) it will be important in future research to address the precise characteristics of the computations performed by this region. Future research will investigate the neural bases of arithmetic processing deficits in individuals with neurodevelopmental disorders known to affect mathematical skills (Curfs *et al.*, 1989; Rovet *et al.*, 1994).

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