

## Regular Article

# Cortical activation during retrieval of arithmetical facts and actual calculation: A functional magnetic resonance imaging study

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### Abstract

By using functional magnetic resonance imaging (fMRI), the neural substrates involved in mental recitation of the single-digit multiplication table and serial subtraction were studied. The former depends mostly on well-learned arithmetical facts, while the latter requires arithmetic processing. Activation during each task was compared with that in a number counting control. During the recitation of single-digit multiplication, the activated regions included the area lying along the left intraparietal sulcus, the premotor and supplementary motor areas, and the posterior portion of the left inferior frontal gyrus. The areas activated during serial subtraction included these areas as well as the bilateral prefrontal and right parietal areas. From the results obtained during retrieval of the multiplication table in this study and previous studies, it was concluded that semantic memory of the multiplication table is stored in the area lying along the intraparietal sulcus and that the frontal areas play an executive role in utilizing the semantic memory of arithmetical facts. It was assumed that the arithmetical facts requiring actual calculation are also stored in the same region. The additional activation during serial subtraction compared with the activation during retrieval of the multiplication table is probably due to the processes of actual calculation. These processes include proper alignment of digits, which may have caused the right parietal activation, and maintaining digits needed for the mental serial subtractions, which may have caused the bilateral prefrontal activation.

### Key words

calculation, frontal lobe, functional magnetic resonance imaging, multiplication, parietal lobe, semantic memory, subtraction.

## INTRODUCTION

Impaired numerical calculation, or acalculia, in brain-damaged patients has been studied for many years.<sup>1,2</sup> Studies of number processing in normal adults, in whom these skills are established, and in young children, in whom they are still being acquired, have made it possible to develop detailed functional models of number processing. It is now established that the ability to perform calculation includes multi-component cognitive functions.<sup>3,4</sup> In calculation, mul-

tiples processes are simultaneously carried out. These include retrieval of a number fact or table value, spatial alignment of digits, procedural access, and retention and use of any integers remaining from the previous product. Studies of brain-damaged patients with arithmetical deficits usually demonstrated deficits in both first, retrieval of number facts or table values, such as those in a multiplication table, and second, the procedures for performing complex multidigit operations. Impairments of these two abilities have been shown to be disassociated in some acalculic patients,<sup>5–8</sup> suggesting that these two operations require interrelated but separate abilities.

While most studies have focused almost exclusively on the functional organization of calculation,<sup>4,9,10</sup> our knowledge of the neural bases of mental arithmetic remains limited. Because acalculia is usually accom-

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panied by aphasia, constructional disability, unilateral spatial neglect, or dementia,<sup>11–16</sup> it is difficult to determine the critical region specific for acalculia in lesion studies. Acalculia may occur in association with parieto-occipital lesions in the left hemisphere.<sup>2,17,18</sup> However, deficits in calculation have reportedly been caused by non-parietal lesions including lesions in the left medial frontal, left and right frontal, left subcortical, and ventral temporo-occipital regions.<sup>7,19–22</sup> The results of lesion studies suggest that the relevant functions are distributed over different cortical areas, and damage to any component could result in a form of acalculia.

Functional neuroimaging such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have been utilized in order to produce functional maps of brain activation during calculation in healthy subjects.<sup>23–27</sup> These studies indicated that the frontal and parietal lobes have a role in calculation. However, the neural bases for each subcomponent of calculation, such as retrieval of arithmetical facts and actual calculations, have not been evaluated. A recent PET study demonstrated that single-digit mental multiplication activated three areas: the bilateral inferior parietal gyri, bilateral supplementary motor area and left precentral gyrus.<sup>25</sup> However, these results might include activations due to the process of verbal production because the authors used the resting state, which is characterized by uncontrolled brain activation, as a control task instead of a proper task. In the present study, we applied fMRI in order to determine the neural substrates involved in mental recitation of the single-digit multiplication table and serial subtraction. The former depends mostly on arithmetical facts because most people memorize the multiplication table in elementary school, while the latter needs arithmetic processing. A comparison of the two operations would elucidate the neural substrates relevant to subcomponents of calculation.

## MATERIALS AND METHODS

### Subjects

The entire procedure for this study strictly followed the Clinical Study Guideline, Ethical Committee, Hyogo Institute for Aging Brain and Cognitive Disorders, 1993, and the Declaration of Human Rights, Helsinki, 1975, and was approved by the Internal Review Board. After complete description of the study to the subjects, written informed consent was obtained.

Nine healthy male volunteers (aged from 24 to 36 years, mean age  $30.3 \pm 4.8$  years) participated in this

study. All were right-handed university students or university graduates and were educated in Japanese elementary schools. All subjects could recite all of the items in the multiplication table ( $2 \times 1, 2 \times 2, \dots, 2 \times 9, 3 \times 1, 3 \times 2, \dots, 3 \times 9, \dots, 9 \times 1, 9 \times 2, \dots, 9 \times 9$ ) by heart.

### Tasks

We gave the subjects three tasks, two activation tasks and one control task, while in the MRI unit. The activation tasks were a serial subtraction and a recitation of single-digit multiplication, and the control task was a number-counting task. Subjects were asked to perform all tasks mentally without speaking or using finger movements. In one session a subtraction task, a number-counting task, and a multiplication task were administered successively for 20 s each. The session was repeated four times using different tasks in each session. For the subtraction task, subjects were asked to sequentially subtract the same number from 100. A different number (16, 17, 18 or 19) to be subtracted from 100 was given at the beginning of each subtraction task. For the single-digit multiplication task, subjects were asked to recite two rows (i.e.  $2 \times 1, 2 \times 2, \dots, 2 \times 9, 3 \times 1, 3 \times 2, \dots, 3 \times 9$ ) in the multiplication table. Two different rows were given for each multiplication task. For the control counting task, subjects were asked to list ordinal numbers in increasing rank from a base number. A different base number (20, 40, 60 or 80) was given for each task. The subjects were asked to perform the tasks as quickly and as accurately as possible. For the subtraction task, the subjects were asked to return to the initial subtraction in each task, before the answer was a negative number. For the single-digit multiplication task, the subjects were asked to repeat from the first item in each task, if they reached the final item.

### Functional magnetic resonance imaging procedures

Imaging was performed with a 1.5 T whole-body MRI scanner (Signa Horizon; General Electrical Medical Systems, Milwaukee, Wisconsin, USA). A receive-transmission whole-head coil was used for signal reception. Head movement was minimized by using a foam pad with each participant's head impression. A parasagittal localizer scan (conventional  $T_1$ -weighted spoiled gradient recalled acquisition in steady state (GRASS) sequence; through-plane resolution = 5 mm thick; 5 slices) was first obtained in order to determine the orientation for the imagings, and then ten 7 mm thick axial images (separated by 0.5 mm gaps) parallel to the anterior-posterior commissure plane were

acquired in order to obtain structural information for co-ordination of the functional scans. A T2\*-sensitive gradient echo type echo planar pulse sequence was used for functional imaging with parameters of time to echo (TE)=60 ms, TR=2000 ms, flip angle=60°, field of view (FOV)=36 cm and inplane resolution = 2.82 mm. The start and stop times of each task were indicated to the subjects through a speaker during a 2-s break preceding acquisition onset. During each functional run, 40 sets of eight 7 mm thick axial images with a 0.5 mm gap from 7.5 to 60 mm above the anterior-posterior commissure plane were acquired parallel to the anterior-posterior commissure plane.

### Data analysis

Image processing was performed on a workstation (Indigo<sup>2</sup> High Impact; Silicon Graphics, Mountain View, CA, USA) by using a commercially available program (Dr View; Asahi Joho System, Tokyo, Japan). All functional runs of each subject were intensity scaled by normalizing the intensities to the mean signal value of the brain. The brain was defined as those pixels whose intensities were more than 10% of the mean signal of all pixel values of all images in one frame so that all mean baseline raw magnetic resonance signals were equal. The first two images of each run were discarded in order to assure that the magnetic resonance signal had reached equilibrium on each slice. A Gaussian filter of 6 mm full width at half-maximum was then applied for all of the functional data in order to enhance the signal-to-noise ratio. For each slice, the functional maps for 'serial subtraction - number counting' and 'recitation of multiplication table - number counting' were generated by a Student's *t*-test analysis with thresholding at  $P < 0.001$ , and the pixels with significantly activated voxels were overlaid on the original echo planar images of each subject. In order to indicate the frequency of activation among the subjects in each activated area, the echo planar images that were averaged for all subjects were superimposed on the areas with significantly activated voxels of each subject. Then, the frequency of activation among the subjects was visualized in each activated area by a color scale.

In order to quantitatively examine the difference in the extent of activation, the frontal lobe (eight sections) and parietal lobe (the upper six sections) were outlined and the ratio of the number of significantly activated voxels to the number of voxels in the frontal or parietal lobe was calculated in each subject. The outlines of the frontal and temporal lobe were decided by the neuroradiologist. The differences in ratios for each lobe were analyzed by two-way

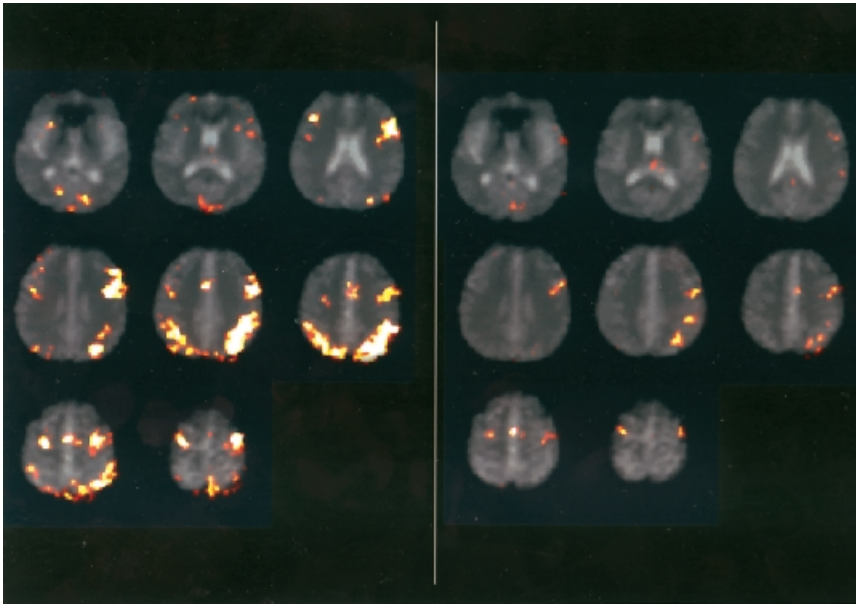
(hemisphere (left-right) X task) analysis of variance (ANOVA) for repeated measures.

### RESULTS

All subjects said after all of the sessions that they could perform all of the tasks without hesitation.

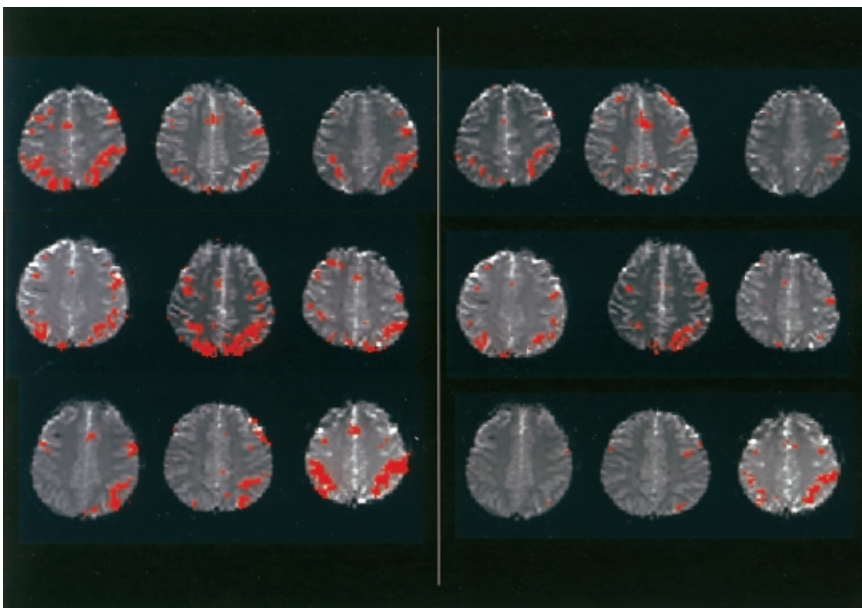
Figure 1 shows the areas among subjects (averaged) that were significantly activated during the subtraction and multiplication tasks, and Fig. 2 plots significantly activated voxels on a slice intersecting the intraparietal sulcus in each subject. During the subtraction task the areas commonly activated included the inferior parietal area, the premotor and supplementary motor areas, the prefrontal area of both hemispheres, and in and the posterior portion of the inferior frontal gyrus, and the inferior parietal area of left hemisphere. The extent of activation was invariably larger in the left hemisphere than in the right hemisphere. During recitation of single-digit multiplication significant activations were observed in the premotor and supplementary motor areas of both hemispheres, and in the posterior portion of the inferior frontal gyrus, and the inferior parietal area of left hemisphere. The extent of activation was invariably larger in the left hemisphere than in the right hemisphere during recitation of single-digit multiplication. For each of the activated areas in each of the subjects the degree of activation during recitation of single-digit multiplication was less than that during serial subtraction. For both tasks, prominent activation was noted in each subject in the area along the intraparietal sulci.

The percentage-activation was expressed as 'the number of significantly activated voxels' / 'the number of voxels included in the frontal or parietal lobe' during the subtraction and multiplication tasks. In the frontal area, the percentage-activation during subtraction was higher than that during multiplication in both hemispheres (Fig. 3a). (The percentage-activation averaged over all subjects was 4.6% vs 2.1% in the left hemisphere and 2.8% vs 1.0% in the right hemisphere.) For both tasks, the percentage-activation was higher in the left hemisphere than in the right hemisphere. The results of ANOVA demonstrated that a task effect ( $F_{1,8} = 15.6, P < 0.005$ ) and laterality effect ( $F_{1,8} = 18.3, P < 0.005$ ) on the percentage-activation were significant but the task X laterality interaction was not significant for the frontal lobe. In the parietal area, the percentage-activation during subtraction was higher than that during multiplication in both hemispheres (Fig. 3b). (The percentage-activation averaged over all subjects was 7.8% vs 2.5% in the left hemisphere and 4.5% vs 1.2% in the right hemisphere.) For both tasks, the



**Figure 1.** Significantly activated areas among subjects (averaged) during the subtraction task (left) and the multiplication task (right). Mean composite images were created from averaged binary images of thresholded t-maps for all subjects and averaged echo planar images for all subjects. The left side of the images corresponds to the right side of the brain. White corresponds to areas with higher ratios of the subjects showing a significant activation and the darker red corresponds to areas with the lower ratio. During the subtraction task, the areas activated in many subjects were the bilateral inferior parietal areas, bilateral premotor and supplementary motor areas, prefrontal area and the posterior portion of the bilateral inferior frontal gyri. When the subject recited the single-digit multiplication table, the areas that were activated were similar to

those activated during serial subtraction, except for the bilateral prefrontal, the right parietal, and the posterior portion of the right frontal areas. However, the areas that were activated during recitation of the single-digit multiplication table were uniformly smaller than those activated during serial subtraction.



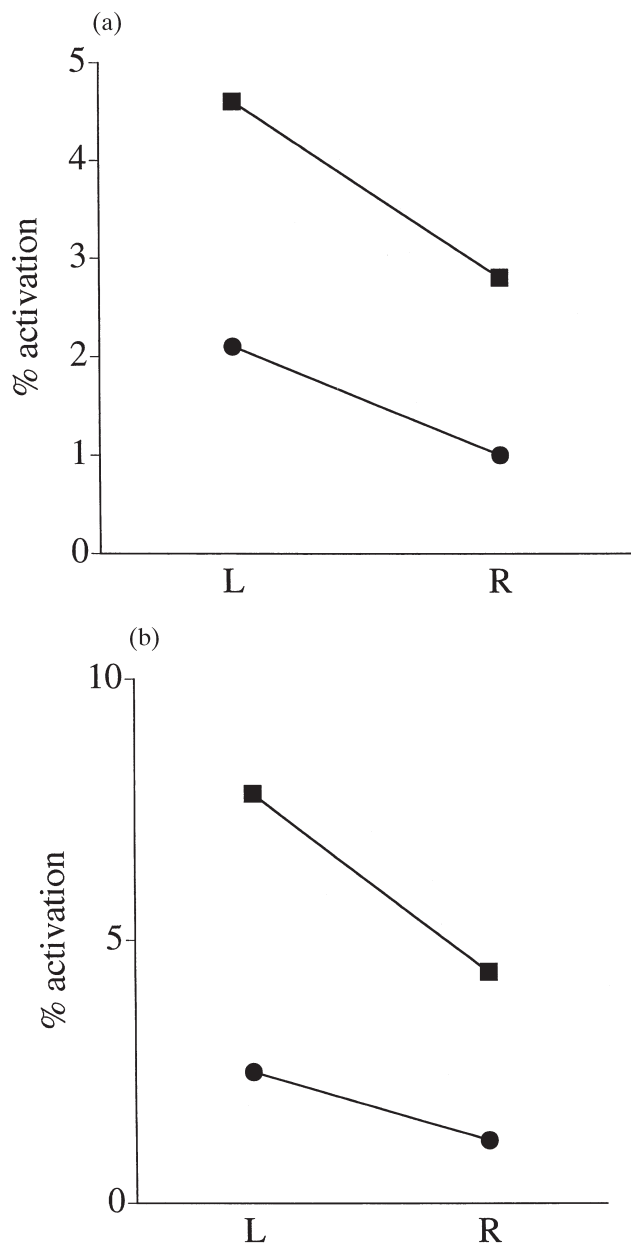
**Figure 2.** Significantly activated voxels during the subtraction task (left) and the multiplication task (right) plotted on slices intersecting the intraparietal sulcus. For each subject, composite images intersecting the intraparietal sulcus were created from binary images of thresholded functional t-maps and the original echo planar images. The left side of the images corresponds to the right side of the brain. Red spots are the areas with significant activation. These images show a prominent activation in the area lying along the left dominant bilateral intraparietal sulcus in both tasks.

percentage-activation was higher in the left hemisphere than in the right hemisphere. The results of ANOVA demonstrated that a task effect ( $F_{1,8} = 18.8$ ,  $P < 0.005$ ) and a laterality effect ( $F_{1,8} = 15.6$ ,  $P < 0.005$ ) on the percentage-activation were significant but the task  $\times$  laterality interaction was not significant for the parietal lobe. In both the frontal and parietal lobes, the extent of activation during subtraction was signifi-

cantly larger than that during multiplication in both hemispheres and larger in the left hemisphere than in the right hemisphere during both tasks.

## DISCUSSION

In this study, we focused on cortical activation during retrieval of table values in the process of calculation.



**Figure 3.** The averaged percentage-activations among the subjects in the frontal lobe (a) or parietal lobe (b) during subtraction (■) and multiplication tasks (●). The percentage-activation was expressed as 'the number of significantly activated voxels'/'the number of voxels included in the frontal or parietal lobe' during the subtraction and multiplication tasks. In both the frontal and parietal lobes of both hemispheres, the percentage-activation during subtraction was higher than that during multiplication. The percentage-activation during both tasks was higher in the left hemisphere than in the right hemisphere. R, right hemisphere; L, left hemisphere.

As Japanese people memorize the multiplication table (from  $2 \times 2$  to  $9 \times 9$ ) in primary school, the table values were considered to belong mostly to semantic memory in our subjects. Recitation of the single-digit multiplication table is a task requiring retrieval of table values from semantic memory. This operation also included the process of verbal production of numbers (articulatory component). In this study, we used number counting, which also included the process of number production, as a control task. Therefore, comparison of the multiplication and number-counting tasks would identify the brain areas that involve only the retrieval of the multiplication tables from semantic memory.

When a subject mentally recited the single-digit multiplication table, the activated area included the regions lying along the left intraparietal sulcus in the inferior parietal area, premotor and supplementary motor areas, and the posterior portion of the left inferior frontal gyrus. Our results indicated that recitation of the multiplication table requires an extensive network that engages both the frontal and parieto-occipital regions. There are some reports of patients with lesions in the left posterior parieto-occipital area who demonstrated impairment of access to arithmetical facts including single-digit multiplication without impairment of actual calculation.<sup>5,6</sup> Cohen and Dehaene documented an apparent loss of stored knowledge in a patient with a selective impairment of memory for addition and multiplication tables.<sup>6</sup> They suggested that the impairment was caused by lesions in the left parieto-temporal lobe. Therefore, it is likely that semantic memory of the multiplication table was stored in the area lying along the left intraparietal sulcus in the inferior parietal area.

The supplementary motor area and premotor area are activated during single-digit mental multiplication,<sup>25</sup> whereas these areas and the left inferior frontal gyrus including Broca's area are activated in several non-numerical tasks including verbal production.<sup>28-31</sup> These findings suggest a relationship between the supplementary motor, premotor and Broca's areas and verbal production. However, Broca's area is activated during tasks requiring the recitation of semantic memory for words, even after canceling out the effects of the articulatory component of verbal production with the subtraction approach, as was also found in this study.<sup>32,33</sup> Moreover, the left frontal area including the supplementary motor area, premotor area and inferior frontal gyrus are activated during language tasks requiring semantic memory for words with little or no requirement for speech production.<sup>34</sup> It has been suggested that frontal activation in language tasks may represent an 'executive' mechanism

facilitating access to a posteriorly located semantic knowledge store.<sup>34,35</sup> According to this hypothesis, the role of the frontal areas in the recitation of the single-digit multiplication table is considered to be an executive operation for semantic memory of the multiplication table. The semantic memory stored in the area lying along the intraparietal sulcus.

During the serial subtraction in the present study, the bilateral inferior parietal area, premotor and supplementary motor areas, prefrontal area, and the posterior portion of the left inferior frontal gyrus were activated in all subjects. The left inferior parietal area was the area that was most commonly and broadly activated. The areas activated during serial subtraction encompassed those areas activated during recitation of multiplication, as well as the bilateral prefrontal and right parietal areas. In contrast to recitation of the multiplication table, which requires only the retrieval of arithmetical facts from semantic memory, mental serial subtraction consists of a sequence of several fundamental operations. In mental serial subtraction, first, the numbers and arithmetical facts involved in the calculation are generated. Second, they are mentally used in arithmetical operations, including borrowing and aligning digits properly. Finally, data are kept on-line for further operations. The additional activation observed in this study reflects the additional processes that are required for serial subtraction. The right inferior parietal area was activated during serial subtraction but not during recitation of the table values. Right posterior lesions may result in visuo-spatial dyscalculia.<sup>36</sup> As one needs to align digits properly in serial subtraction, the right inferior parietal lobe most likely plays a role in this process.

Most previous studies on brain-damaged patients with arithmetical deficits have stressed that the lesions that result in acalculia involve the left inferior parietal area or the left parieto-occipito-temporal junction.<sup>2,5,17</sup> However, in this study the area activated during serial subtraction was not the parieto-occipito-temporal junction but the area lying along the left intraparietal sulcus covering the inferior part of the superior parietal lobule. Takayama *et al.*<sup>18</sup> studied three patients with isolated acalculia and found that the overlapping areas of their lesions covered the area lying along the left intraparietal sulcus. Our study is consistent with the lesion study and, taken together, our study and the lesion study suggest that the area lying along the intraparietal sulcus plays the most important role in actual calculation.

Working memory must be involved in maintaining numbers during mental subtraction and for further calculations. The prefrontal cortex has been shown to

be involved in working memory.<sup>37,38</sup> In the premotor and supplementary motor areas and the posterior portion of the inferior frontal gyrus, the extent of activation during serial subtraction was wider than that during the recitation of the single-digit multiplication table. It has recently been proposed that Broca's area and the premotor cortex are associated with active maintenance of information in working memory.<sup>39-41</sup> Therefore, activation in the frontal area during serial subtraction in this study was considered to reflect the operation of working memory.

In this study we elucidated the difference between the brain areas activated during actual calculation and during retrieval of arithmetical facts. By using fMRI the neural bases for subcomponents of calculation other than retrieval of arithmetical facts can be evaluated.

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