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Introduction

A number of neuroimaging studies on memory systems in humans have revealed that specific regions are associated with encoding or retrieving experienced episodes, i.e., events of the past[1-5]. There may be another type of memory which we need in everyday life. This is called prospective memory and is defined as an ability to remember future plans[6]. This ability of not forgetting to do a necessary task at a certein time in the future has been suggested to be associated with activities of the frontal lobes[7-9]. The aim of this study is to investigate possible neural basis involved in prospective memory using the neuroimaging technology of PET.

Methods

Subjects

Six healthy young male volunteers participated. All subjects were right handed. A written informed consent was obtained from each subject.

Task design

Subjects performed two tasks, i.e., a control task and an experimental task, which were arranged to be preceded by a pre-scan learning period and to be followed by a post-scan recall period. The subjects repeated both tasks in random order. In a learning period, the subjects were auditorily presented with the lists of 10 stimuli of Japanese noun words three times in a row and were required to retain these words as target stimuli throughout the PET scan. In a recall period immediately after the PET scan, the subjects were asked to recall the 10 stimuli. In a scan period, the subjects heard a set of 5 stimuli of Japanese noun words from a tape recorder through a pair of earphones in the rate of one word per second and were required to repeat orally the set of stimuli within a blank duration of 7 seconds. The subjects repeated this sequence 10 times during the scan. Further, only in the experimental task, list of stimuli was set to include the target stimuli with very low frequency (2 or 3 times during whole list) and the subjects were instructed to notice if one of them appeared or not. If it appeared, the subjects had to tap their left hand while repeating it orally.

Scanning Methods and Regional Analysis

Regional cerebral blood flow (rCBF) was measured using PET (SET2400W, Shimadzu) and ^{15}O labeled water (approximately 35 mCi for each injection). Subjects had a catheter placed into the right brachial vein for tracer administration, closed their eyes, and wore an individual stereotaxic fixation helmet. Each PET data acquisition started at the time of bolus injection and the start of word repetition task, and lasted 120 sec. All rCBF images were transformed into the standard anatomical format using Human Brain Atlas System[10] and each subject's MRI. Then all standardized rCBF images were smoothed with a three dimensional Gaussian filter 10mm in wide and normalized for global cerebral blood flow of 50 ml per 100 g per min[11-12]. The comparison between the control task and the experimental task was performed by 2 way analysis of variance (ANOVA, two tasks and six subjects as factors). Namely, image of F- values for differences between tasks was calculated on a voxel by voxel basis and voxels with F-values >11.8 ($p<0.005$) were considered to represent regions of significantly increased rCBF. Each activation was superimposed onto the average reformatted MRI of the six subjects. Finally, anatomical localization of areas of activation was estimated in relation to this MRI.

Results

Behaviorally, the mean rate of the subjects' averaged performance of repetition of words in the experimental task was 0.77 and one in the control task was 0.81. The mean rate of successful execution of tapping the left hand during the experimental task was 0.63.

When compared with the control task, regions with significantly increased rCBF during the experimental task were as follows (Table 1, Fig. 1); the left superior frontal gyrus (Brodmann Area, BA 10), anterior cingulate gyrus (BA 24), parahippocampal gyrus (BA 28), the right inferior frontal gyrus (BA 47), middle frontal gyrus (BA 8, 9) and medial frontal lobe (BA 8).

Discussion

Our results provide an evidence that frontal lobe is related to processes involved in prospective memory. The activations of the prefrontal and hippocampal areas may reflect mental processes of memory for the future plan, i.e., tapping the left hand in response to the target item memorized before, during the routine task of word repetition. We suppose that the results may mainly be associated with a process of retention of the encoded behavioral plan, because retrieval and execution of the plan rarely occurred during the task.

In preceding neuroimaging studies, the lateral frontal lobes were activated in relation with encoding and retrieval of episodic/semantic memory[13)], and with working memory paradigm[14-15)]. Our experimental design seems similar to dual task paradigm of working memory. The lateral frontal activation might be related to the temporary retention and reference of primarily stored information.

On the other hand, activations of the medial frontal region were reported during attention shifting task like Stroop test[16-17)]. Frequent checking whether a presented item is the target or not requires frequent shift of attention, which might have caused the medial frontal lobe activation in the present study.

Another important finding in the results is the left hippocampal activation. In our preceding PET study, we reported that activation of the left parahippocampal region was associated with non-matching to sample strategy of verbal recognition[18)]. In connection with this result, neurophysiological study also showed that the hippocampal regions were involved in novelty detection of non-verbal materials[19)]. We suppose that the same mechanism underlies the left hippocampal activation in the present study, because our experimental task clearly involved a number of non-matching to sample operations (i.e., novelty detection) than matching operation.

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Table 1. Activation foci during the experimental task.

	Anatomical structures	Talairach coordinates x	y	z	peak F-value
Left	Anterior cingulate gyrus (24)	-10	32	8	26.3
	Superior frontal gyrus (10)	-11	66	14	33.9
	Parahippocampal gyrus (28)	-20	-16	-9	19.9
Right	Inferior frontal gyrus (47)	34	18	-16	62.1
	Middle frontal gyrus (9)	35	26	38	13.5
	Middle frontal gyrus (8)	31	12	51	20.0
	Medial frontal lobe (8)	0	40	41	19.1

Regions with significantly increased rCBF during the experimental task compared with the control task. Stereotaxic coordinates refer to the maximal activation indicated by the highest F-values in a particular cerebral structure. Distances refer to the stereotactic space defined by Talairach and Tournoux[20]. Numbers in parenthesis refer to Brodmann areas.

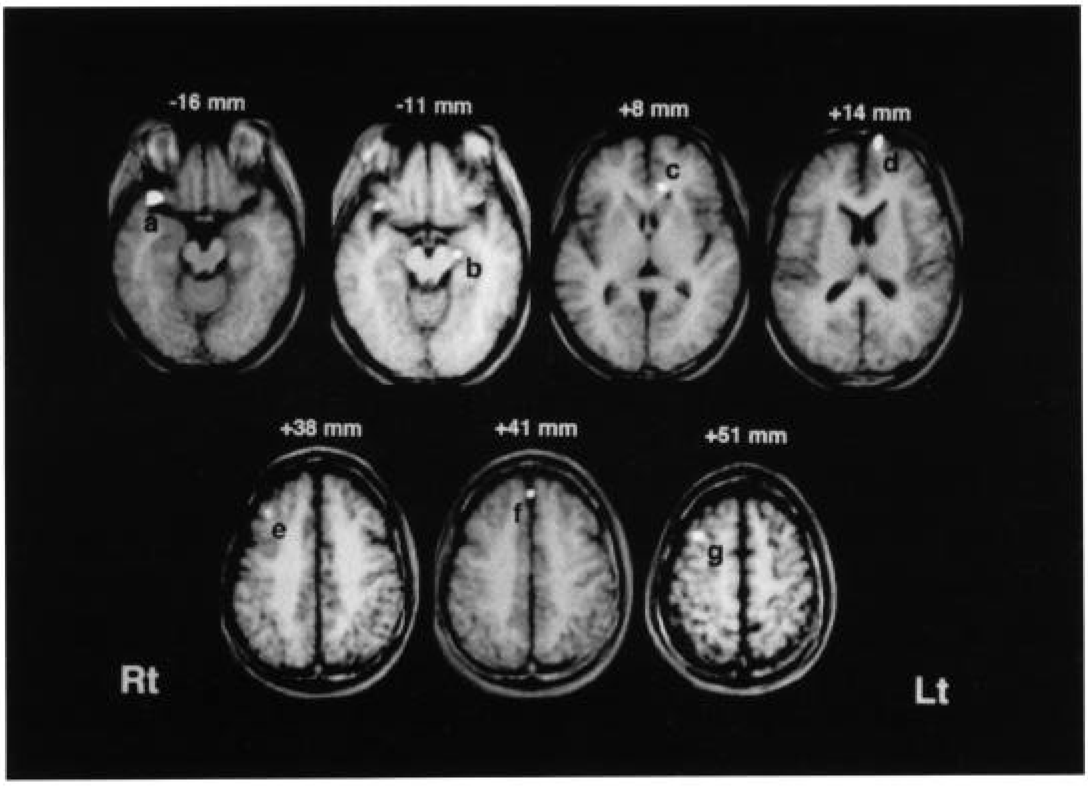

Figure 1. Significantly activated areas ($F>11.8$, $p<0.005$) during the experimental task superimposed onto axial sections of averaged MRI of the subjects. Each section's distance from AC-PC line was noted above each section. The left side of the section refers to the right side of the brain. a) The right inferior frontal gyrus (BA 47), b) the left parahippocampal gyrus (BA 28), c) the anterior cingulate gyrus (BA 24) and part of the corpus callosum, d) the superior frontal gyrus (BA 10), e) the right middle frontal gyrus (BA 9), f) the medial frontal lobe (BA 8), g) the right middle frontal gyrus (BA 8).