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Participation of the prefrontal cortices in prospective memory: evidence from a PET study in humans

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Abstract

Prospective memory is a memory feature in humans which involves activities for remembering to do something in the future. The present study provides functional neuroanatomy of prospective memory for the first time. We used positron emission tomography (PET) and found several localized brain activations in relation to a prospective memory task required to retain and remember a planned action while performing an ongoing routine activity. Activations were identified in the right dorsolateral and ventrolateral prefrontal cortices, the left frontal pole and anterior cingulate gyrus, the left parahippocampal gyrus, and midline medial frontal lobe. We attributed these activations to several cognitive processes involved in prospective memory, such as holding an intention toward future behavior, checking target items within presented stimuli, and dividing attention between the planned action and the routine activity. © 1998 Elsevier Science Ireland Ltd. All rights reserved

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The memory process we need most in everyday life is that of not forgetting to do something at an appropriate time in the future. This aspect of memory has been termed prospective memory, i.e. memory of future plans or remembering what we must do, in contrast with retrospective memory, i.e. memory of past events or remembering what we have done [5,13]. Despite its importance, knowledge of cerebral mechanisms involved in prospective memory has remained scanty. In a few studies, impairments of prospective memory have been observed in patients with dementia [12] or frontal lobe lesions [2]. These data, however, lacked strict neuroanatomical correlations.

The aim of the present study is to elucidate precise neural basis involved in prospective memory by using recent neuroimaging technology. We measured rCBF of young normal subjects by ^{15}O-labeled water ($H_2^{15}O$) PET while performing a prospective memory task and a control task.

Six right-handed healthy male volunteers (age ranging from 19–24 years, mean 21.5 years) participated in the study. They all gave their written consents in accordance with guidelines approved by Tohoku University and the Declaration of Human Rights, Helsinki, 1975. In the experiment, the subjects were required to perform the prospective memory task and the control task which had three isolated periods, i.e. a pre-PET scan period, a PET scan period and a post-PET scan period (Fig. 1). Japanese nouns were auditorily presented as stimuli in the pre-PET scan period and the PET scan period. During the pre-PET scan period, a list of 10 stimuli which appeared at a rate of one per 3 s was presented three times in a row. The subjects were required to memorize them as target stimuli and were also instructed to retain these words through the PET scan period which

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followed within 3 min. During the PET scan period, ten sets of five stimuli which appeared at a rate of one per second were presented with an inter-set blank duration of 7 s (see the bottom of Fig. 1). The subjects heard a set and were required to orally repeat it within the blank duration. The subjects repeated this sequence 10 times during the PET scan period. In the post-PET scan period, the subjects were asked to recall the 10 target stimuli which they had retained. All procedures mentioned above were identical in both prospective memory task and control task. Only in the prospective memory task, however, the subjects were informed beforehand that the stimuli they had to repeat in the PET scan period were set to include the target stimuli with very low frequency (two or three targets within 50 stimuli). They were requested to pay attention to the appearance of the targets and to tap with their left hand when they repeated the targets orally. In the control task, no targets were included in the stimuli of the PET scan period. The subjects performed each task twice and the ordering of the tasks was counterbalanced across the subjects.

Our prospective memory task was arranged after the manner of an in-laboratory paradigm developed by Einstein and McDaniel [7] in order to realize an experimental situation which reflected mental processes of prospective memory, i.e. holding an intention to perform a prospective action (tapping with the left hand) while performing a routine task (word repetition) and remembering the intention in response to an appropriate event (appearance of a target item). In the prospective memory task, the subjects were required not only to engage in immediate word repetition but also to pay attention to the appearance of the targets, as well as to hold an intention to perform the prospective action. In the control task, the subjects were also required to engage in word repetition, holding the targets in mind. However, they were not required to pay attention to the appearance of the targets and performance of the prospective action was not required in this condition. Thus, comparing rCBFs during the two tasks would reveal the areas associated with several important aspects of mental processes for prospective memory, such as holding an intention or controlling attention.

The rCBF was measured by using PET (SET2400W Shimadzu, FWHM 4.0 mm) and ^{15}O labeled water ($H_2^{15}O$, approximately 35 mCi for each injection) with a transaxial sampling field of view (FOV) of 256 mm and an axial FOV of 190 mm. Slice thickness was 3.125 mm. Each PET data acquisition and the PET scan period of the tasks started at the same time of bolus injection of $H_2^{15}O$, and lasted 120 s. Prior to the PET measurements, a transmission scan was performed and these data were used to obtain corrected emission images. All PET acquisition data were reconstructed by using a convolution filter (cut-off value of 8 mm). During the measurements, subjects had a catheter inserted into the right brachial vein for tracer administration and wore an individual stereotaxic fixation helmet. A T1-

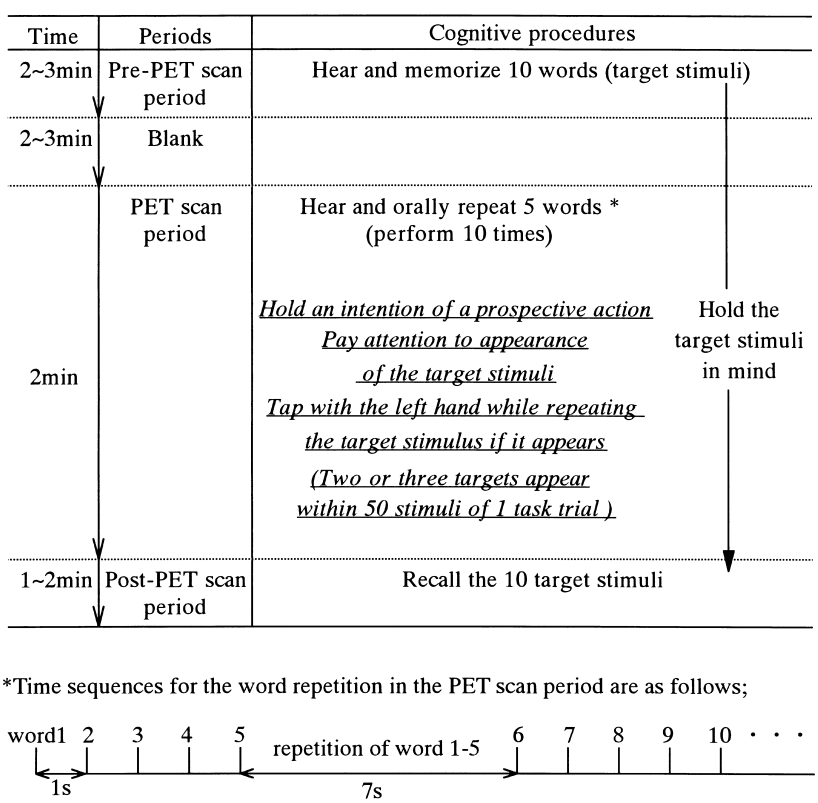

Fig. 1. Schematic representation of experimental procedures. A time course of experimental periods is indicated. Cognitive components specific to the prospective memory task are underlined. The other procedures are common in both prospective memory and control tasks. In the bottom of the figure, the first two sequences for the routine activity of word repetition in the PET scan period are depicted.

weighted magnetic resonance image (MRI) of each subject's brain was obtained on a separate occasion.

All rCBF images were transformed into the standard anatomical format using the Human Brain Atlas System [17] and each subject's MRI. The standardized rCBF images were then smoothed with a three-dimensional Gaussian filter 10 mm in width and normalized for global cerebral blood flow of 50 ml/100 g/min [10,16]. For comparison of the prospective memory task with the control task, two-way analysis of variance (ANOVA, two different tasks and six subjects as factors) was performed on a voxel by voxel basis and an image of *F*-values for task difference was calculated. We regarded voxels with *F*-values >11.8 ($P < 0.005$) as significant. Finally, each activation was superimposed onto a mean reformatted MRI of the six subjects. We identified the anatomical structure and the Brodmann area of each activation by referring to atlas of the Talairach and Tournoux [18].

The mean rate of successful repetition of words in the prospective memory task (0.77) was significantly lower ($P < 0.01$) than that in the control task (0.81). The mean numbers of words correctly recalled during the post-PET scan period were high and not significantly different between the two tasks (0.91 for the prospective memory task and 0.93 for the control task). Two of the six subjects perfectly performed the prospective action in both of two sessions. The others failed once to thrice for the total of five targets over the two sessions. The mean rate of success was 0.65. When later asked whether they had forgot the prospective task occasionally during the scan, they confirmed they never forgot what to do.

In the image of *F*-values, several highly localized frontal and medial temporal activations during the prospective memory task compared with the control task were observed (Fig. 2), i.e. the right dorsolateral prefrontal cortices (Brodmann Areas, BA 8 and 9), right ventrolateral prefrontal cortex (BA 47), left frontal pole (BA 10), left anterior cingulate gyrus (BA 24), midline medial frontal lobe (BA 8), and left parahippocampal gyrus (BA 28). All these regions showed increase of rCBF in both trials of the prospective memory task in all subjects.

As far as we know, this is the first functional neuroanatomical data which provides a clear evidence that the frontal lobes are associated with mental processes of prospective memory. Theoretically, prospective memory is thought to be comprised of successive phases of (1) making and encoding future plans, (2) holding the plans for a while, (3) retrieving and executing the plan in association with the encoded context, and (4) evaluating outcome of the executed actions [8]. In this theoretical frame, our experimental design focused mainly on the process of holding the intended behavioral plan. Although our data include the data of the four subjects whose prospective performance was not perfect, we believe that rCBF patterns in these subjects were also related to prospective memory processes for two reasons. One is the subjects' confirmation that they never forgot the task itself during the session. Second is a fact that even in these subjects same areas were active as those with the perfect performers. We suppose the activated areas are most likely associated with holding of an intention. Other related processes like retrieval or execution of a plan might not have been well reflected in our results, since the number of targets was set to be very low because of the time constraint of a PET scan, and also the subjects' performance was not always perfect.

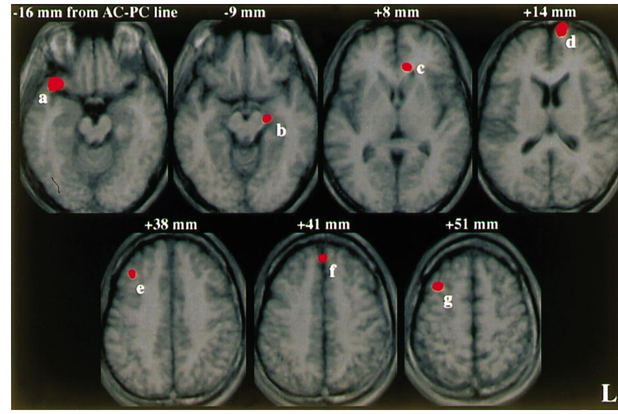

Fig. 2. Red areas indicate significantly activated regions ($P < 0.005$ in ANOVA) during the prospective memory task compared with the control task. All are superimposed onto the mean reformatted MRI of the six subjects (axial section). Distance from AC–PC line was noted above each section. The left side of the section refers to the right side of the brain. (a) The right inferior frontal gyrus (BA 47; *x*, *y*, *z* in Talairach coordinates [18] = 34, 18, –16; peak *F*-value = 62.1), (b) the left parahippocampal gyrus (BA 28; *x*, *y*, *z* = –20, –16, –9; *F* = 19.9), (c) the left anterior cingulate gyrus (BA 24; *x*, *y*, *z* = –10, 32, 8; *F* = 26.3), (d) the left superior frontal gyrus (BA 10; *x*, *y*, *z* = –11, 66, 14; *F* = 33.9), (e) the right middle frontal gyrus (BA 9; *x*, *y*, *z* = 35, 26, 38; *F* = 13.5), (f) the medial frontal lobe (BA 8; *x*, *y*, *z* = 0, 40, 41; *F* = 19.1), and (g) the right middle frontal gyrus (BA 8; *x*, *y*, *z* = 31, 12, 51; *F* = 20.0).

Of the activated frontal regions in our results, dorsolateral prefrontal activations were often reported in the study concerning working memory [3,4,15]. In these studies, the activations were assumed to be related to the dual cognitive operations [4] (BA 9 and 46, bilaterally) or the active maintenance process of information [3,15] (areas 9/46 and 44). The right middle frontal gyri (areas 8 and 9) activated in this study are included in these regions. In our task arrangement, a component specific to working memory, i.e. dual cognitive operations, was included in both prospective memory and control tasks. The subjects were required to repeat words while holding target words at the same time in both tasks. If the same loads were placed on working memory, statistical analysis would cancel out activations related to working memory. However, our prospective memory task placed an additional load on working memory, that is, holding a plan. The right middle frontal activation might reflect this additional load. As compared with the previous neuroimaging data related to working memory, however, slightly different lateral prefrontal regions were also activated in our study, such as the left frontal pole (area 10) and the right ventrolateral prefrontal region (47). We assume that the activations of the left area 10 and the right area 47 are more essentially related to the process itself of holding intention of future behavior, which is the main difference between our two tasks. The importance of these regions is also suggested by the fact that the peak *F*-values of these activations were the highest in each hemisphere.

Activation of medial frontal regions has been reported with an attention shifting task like the Stroop test [1,14]. Although the location of activated medial frontal lobes was not exactly the same between these studies and ours, our results can be explained in light of attention control. When the stimuli were presented, the subjects had to divide their attention between two different cognitive operations, one for repeating words and the other for checking the targets and tapping with the left hand, possibly causing the medial frontal activation seen in the present study. Behavioral data on word repetition also suggested that the subjects paid certain amount of attention for the appearance of the targets during the prospective memory task, as compared with the control task.

Another important finding is left parahippocampal activation. In a previous PET study, we reported that left parahippocampal activation was associated with non-matching to sample strategy in a verbal recognition task [9]. More recently, Dolan et al. [6] showed that the left medial temporal region was activated by a paired-associated learning task, when a pair of presented words was novel. An electrophysiological study showed that the hippocampal regions were involved in novelty detection of non-verbal materials [11]. We suppose that the left parahippocampal activation in the present study reflects a process of novelty detection which is essential for checking of the targets. In our prospective memory task, subjects were required to check whether the presented words were same or different from the target ones, and, as a consequence, they performed a great number of novelty detection operations because of the rare appearance of the target items. In the control task, however, no active checking of the words was required.

In summary, our results demonstrate that the networks involving the right dorsolateral and ventrolateral prefrontal cortices, the left frontal pole and the medial frontal regions and the left parahippocampal region provide the anatomical basis for prospective memory. Based on theoretical background, our neuroanatomical findings seem to correspond to some of the multiple components involved in prospective memory, that is, holding intention of what we will do in the future mediated by the right ventrolateral prefrontal region and the left frontal pole, checking the novelty of the presented stimuli by the left parahippocampal region, and dividing attention between performing the intended plan and the routine activity by the medial frontal regions. Although the processes of retrieval and execution of planned action could not be well assessed in the present study, our findings indicate other important memory functions mediated by the prefrontal cortices, besides functions concerned with working memory or episodic/semantic memory.

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