Functional roles of the cingulo-frontal network in performance on working memory

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We examined the relationship between brain activities and task performance on working memory. A large-scale study was initially administered to identify good and poor performers using the operation span and reading span tasks. On the basis of those span scores, we divided 20 consenting participants into high- and low-span groups. In an fMRI study, the participants performed verification of arithmetic problems and retention of target words either concurrently or separately. The behavioral results showed that performance was better in the high-span group than in the low-span group under a dual-task condition, but not under two single-task conditions. The anterior cingulate cortex (ACC), left prefrontal cortex (PFC), left inferior frontal cortex, and bilateral parietal cortex were primarily activated for both span groups. We found that signal changes in the ACC were greater in the high-span group than in the low-span group under the dual-task condition, but not under the single-task conditions. Structural equation modeling indicated that an estimate of effective connectivity from the ACC to the left PFC was positive for the high-span group and negative for the-low span group, suggesting that closer cooperation between the two brain regions was strongly related to working memory performance. We conclude that central executive functioning for attention shifting is modulated by the cingulo-frontal network.
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Introduction

The working memory system, which consists of some domain-specific storage components and a domain-general central executive, is involved in higher level cognition such as reading comprehension, mental arithmetic, and goal-oriented behavior (Baddeley, 1986). It has been proposed that the central executive plays an important role in the regulation of storage components, active maintenance of the task-relevant goal, and inhibition of disruptive input (Baddeley and Logie, 1999). Engle et al. (1999) indicated that predictive power of correlations between working memory tasks and complex cognitive tasks is derived from central executive functioning using structural equation modeling (SEM). Neuroimaging studies have demonstrated that the executive processes are mediated by the frontal lobe, particularly the anterior cingulate cortex (ACC) and the prefrontal cortex (PFC) (D'Esposito et al., 1995; Duncan and Owen, 2000; Osaka et al., 2003; Smith and Jonides, 1999). However, there are few studies using working memory tasks that show any significant correlation with complex cognitive tasks, although simple memory tasks or delayed matching-to-sample tasks have been employed within the framework of working memory. Previous studies found that the operation span and reading span tasks are more highly correlated with reading comprehension than short-term memory tasks such as the word span task and the digit span task (Daneman and Carpenter, 1980; Turner and Engle, 1989). The present study examines the relationship between brain activities and performance on the working memory task from the perspective of regions of interest (ROIs) analysis and path analysis.

It has been emphasized that the ACC and PFC are important components of the distributed attentional network (Posner and Petersen, 1990). Some researchers have argued that activations of the PFC and ACC reflect cognitive processes such as memory loading of working memory tasks and inhibition of prepotent responses. Rypma et al. (1999) demonstrated that the bilateral PFC and ACC were activated when participants were asked to retain six letters, but not one or three letters. Barch et al. (1997) showed that a transient increase in signal changes was observed in the ACC as the difficulty of the delayed matching-to-sample task increased, while Bunge et al. (2001) pointed that the ACC's signal intensity was significantly correlated with memory load using the delayed response task. Bush et al. (1998) found that the ACC was activated under response conflict situations such as a Stroop task, in which the word "red" was presented in green type, after which participants had to name the color. The results showed that reaction time (RT) of the current task and signal intensity in the brain region

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decreased with practice, suggesting that activations of the ACC are related to allocation of attentional resources.

Activations of the ACC and PFC were also observed during working memory tasks that included processing and storage components. Bunge et al. (2000) used the reading span task to examine the relationship between activation areas and central executive functioning for coordination of two component tasks. Under a dual-task condition, participants were asked to judge whether visually presented sentences were correct while simultaneously retaining the final word of each sentence. Participants also separately performed each of the two component tasks as a single-task condition. The dual-task condition showed robust activations of the bilateral PFC, ACC, left inferior frontal cortex (IFC), and left parietal lobe, but there were no differences of activation areas between the dual-task and single-task conditions. In addition, the signal intensity of the PFC was higher under the dual-task condition than under the single-task condition. Bunge et al. (2000) concluded that the PFC is activated even under the single-task condition when the memory load exceeds the capacity limit of the IFC related to short-term retention of verbal information.

Smith et al. (2001) compared brain activities of good performers with those of poor performers using the operation span task. The current task had participants verify whether arithmetic problems were correct while concurrently retaining target words. The results showed that the left PFC was activated for poor performers but not for good performers, suggesting the possibility that the activation reflected differences in sensitivity to cognitive demands under a dual-task condition. Osaka et al. (2003) used the listening span task to estimate the correlation of time-series fMRI data between the ACC and left PFC. In the listening span task, participants had to judge whether auditorily presented sentences were correct while retaining the first words of each sentence. The results demonstrated that the correlation coefficient was greater for good performers than for poor performers, thus indicating that the synchronization of the ACC and left PFC contributed to prediction of task performance.

However, several unresolved problems remain. It is unclear how brain activities caused by other executive functions are associated with working memory performance, although Osaka et al. (2003) argued that the activations of the ACC and PFC were linked to the executive function for inhibiting irrelevant information because sentence verification and word retention within the listening span task are interdependent. Smith and Jonides (1999) assumed that the ACC and PFC are the neural bases of executive functions, particularly inhibition of irrelevant input and shifting of attention, and they proposed five types of central executive functioning that were broadly agreed on by many researchers. The present study used the operation span task to examine the relationship between brain activities and shifting of attention between two component tasks: arithmetic verification and word retention. Miyake et al. (2000) pointed that the operation span task is strongly related to central executive functioning for shifting of the mental set and updating of internal representation, which require the ability to switch the focus of attention between concurrent cognitive processes, and to replace old representation with new task-relevant input, respectively. Previous studies found that arithmetic verification is related to activations of the superior parietal lobule (SPL) (Dehaene et al., 1999; Chochon et al., 1999; Rickard et al., 2000; Zago et al., 2001), whereas word retention based on the phonological loop is associated with the left IFC (Awh et al., 1996; Paulesu et al., 1993; Poldrack et al., 1999). However, given that the central executive includes the domain-general characteristics, it was predicted that

differences between dual-task and single-task conditions would reflect brain activities in the ACC and/or PFC, despite the nature of working memory tasks.

There may arise potential criticism of the theory that central executive functioning is supported by not only the ACC and PFC, but also the posterior brain, and that correlation between activities of other brain regions is also greater in good performers than in the poor performers. However, it is unclear how activities of multiple brain regions are linked with working memory performance. We used SEM to construct the best fitting network model that can account for time-series fMRI data of ROIs. SEM can provide a path analytical model in which parameters are represented as intercorrelations between ROIs and evaluate the goodness of fit to the structural models. There have been a few substantial studies in which SEM was applied to fMRI data on visual attention (Büchel and Friston, 1997), object-location learning (Büchel et al., 1999), semantic decision (Bullmore et al., 2000), and auditory processing (Gonçalves et al., 2001), but the issue of comparing a network model of good performers with that of poor performers has not been addressed. However, Duncan et al. (2000) suggested that general intelligence is based on a specific frontal network, beyond different spatial and verbal domains. It was expected that cooperation between the ACC and PFC, rather than posterior brain regions, would be important in predicting working memory performance, even when taking the inter-region network into account.

The major goals of the present study were to examine how brain activities are associated with individual differences in working memory performance and identify whether there was a specific brain activity related to dual-task condition, compared with single-task condition. We used the operation span task to compare brain activations of good performers with those of poor performers under dual-task and single-task conditions, respectively. As discussed above, the operation span task is assumed to include central executive functioning for switching of attention, which affects working memory performance. No part of the study by Smith et al. (2001) included group analyses that were based on large-scale behavioral data. In contrast, we initially administered a pilot study to carefully select good and poor performers for a subsequent fMRI study, in which the participants performed arithmetic verification and word retention tasks either concurrently or separately. Task-related activations for each group were clarified, and signal intensity in ROIs was computed. Finally, path models for the good and poor performers were constructed to compare an estimate of effective connectivity between the ROIs using SEM.

Materials and methods

Participants

Twenty-one healthy students (11 males and 10 females) participated in the fMRI experiment after providing informed consent. Their ages ranged from 22 to 27 years, with an average of 23.6. All the participants who were recruited from a sample of 152 undergraduate and graduate students at Kyoto University were native speakers of Japanese and right-handed. For one male participant, head movement in the scanner was greater than 1 mm, thus we finally analyzed data from 20 participants. The fMRI study was approved by the Institutional Review Board at Advanced Telecommunications Research Institute International, Kyoto, Japan.

We used the operation span and reading span tasks to assess participants' working memory capacity for concurrent processing and storage of information. The working memory tasks were significantly correlated with verbal cognitive abilities (Daneman and Carpenter, 1980; Engle et al., 1999; Turner and Engle, 1989). On the basis of span scores derived from the working memory tasks, participants were divided into two groups of good and poor performers. The operation span task included a set of pairs of arithmetic problems and target words. Participants were instructed to judge whether the arithmetic problems [e.g., $(2 \times 3) - 1 = 5$] were correct as quickly and accurately as possible while simultaneously retaining the target words. In the reading span task, participants had to read aloud a set of unrelated sentences, one at a time, and to retain the underlined word in each sentence. For the two span tasks, the stimuli were visually presented in set sizes ranging from two to five at random, with five trials for each set size. At the end of the trial, participants were asked to recall the target words in serial correct order. The behavioral index was the maximal span of correctly answered items. Mean span scores of all the participants were 3.19 (SD = 0.77) for the operation span task and 2.95 (SD = 0.83) for the reading span task, and correlation between the two span scores was significant [$r(150) = 0.55$, $P < 0.01$]. We obtained 18 and 24 candidates for the high- and low-span groups who had two span scores ranging from 4.0 to 5.0 and from 2.0 to 2.5, respectively. After this screening, 21 of those without psychiatric or neurological history participated in the fMRI experiment. Mean scores of the operation span and reading span tasks were 4.05 and 4.30 for 10 high-span participants and 2.45 and 2.45 for 10 low-span participants, respectively.

Behavioral tasks

In the fMRI experiment, participants performed two scans (13 min 9 s for each) including three different types of cognitive tasks: Arithmetic + Memory, Arithmetic, and Memory conditions. The Arithmetic + Memory and Arithmetic/Memory conditions corresponded to the operation span task and two component tasks, respectively. The presentation order of task epochs was fixed, as indicated in Fig. 1. Each task epoch was repeated four times within the scan, which was interlaced with 24-s baseline epochs. Task epochs of word recognition were established to identify participants' answers.

Arithmetic + Memory condition

Five arithmetic problems and five target words were alternately presented in each epoch. On the basis of the study by Turner and Engle (1989), the arithmetic problems consisted of two operations with an answer [e.g., $(7 \div 2) + 4.5 = 8$; $(2.5 \times 3) - 1.5 = 5$]. The first operation was a multiplication or a division problem in parentheses, whereas the second operation was an addition or a subtraction problem. The first and/or second operations included the value 0.5, and the final answers ranged from 0.5 to 9.5. Half

of the answers were correct and the others were incorrect by 1. The target words were selected from nouns (excluding proper nouns) which were all two Kanji-characters long, with the number of moras adjusted from three to five units. The words were carefully controlled in terms of frequency, concreteness, and familiarity.

The arithmetic problems were presented for 4 s, then the words were presented for 2 s in the same position where the arithmetic problems had appeared. Participants were instructed to solve the arithmetic problems as accurately as possible and retain the target words using rote rehearsal. We used two response boxes with two buttons to acquire participants' responses. Participants pressed the buttons with either the index finger of their left or right hands to indicate whether the arithmetic problems were correct. At the end of the task epoch, five arrays containing three candidate words and one asterisk were presented from left to right for 3 s each. Participants were asked to remember the target words in serial order and respond with the index and middle fingers of their hands, and when there was a target word among these candidates, participants had to indicate the word by pressing the appropriate button. If the target word was not presented, participants pressed a button corresponding to the asterisk. The chance of correctly guessing the answer in word recognition was 25%.

Arithmetic and Memory conditions

It was desirable that the amount of visual input and motor response under the Arithmetic and Memory conditions would be equivalent to that under the Arithmetic + Memory condition. Under the Arithmetic condition, participants were instructed only to perform arithmetic verification, thus five arithmetic problems were presented in sequence, although this time the target words were replaced by a row of asterisks. Under the Memory condition, arithmetic problems were replaced by a row of arrows indicating left or right, and five words were successively presented. Participants pressed the index finger button on the left or right box according to the direction of arrows while concurrently retaining the target words. At the epochs of word recognition, participants were asked to respond by pushing the appropriate button in serial order, as well as under the Arithmetic + Memory condition. Stimulus duration and acquisition of participants' responses under the Arithmetic and Memory conditions were the same as those under the Arithmetic + Memory condition.

Under the baseline condition, a row of arrows indicating left or right was successively presented for 4 s each. Participants had to press the index finger button on the left or right box according to the direction of arrows.

fMRI data acquisition

A time-series of 263 volumes for each scan was acquired using a single-shot echo-planar imaging sequence with a 1.5-T MRI scan-
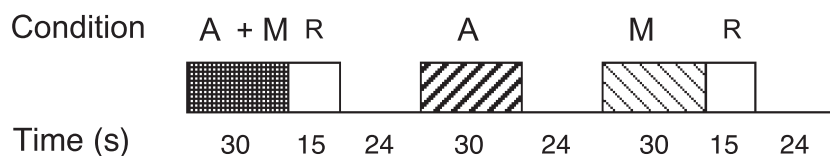

Fig. 1. Block-design paradigm in the fMRI study. A + M: Arithmetic + Memory, A: Arithmetic, M: Memory, R: word recognition.

Table 1
Performance in word recognition and arithmetic verification for high- and low-span groups

Condition	High-span group		Low-span group	
	M	SD	*M*	SD
Arithmetic + Memory				
Word recognition (%)	95.3	3.0	81.3	6.9
Reaction time (ms)	1324	206	1446	143
Arithmetic verification (%)	89.5	6.8	83.3	10.3
Reaction time (ms)	2416	307	2763	322
Arithmetic				
Arithmetic verification	88.5	5.7	81.5	10.7
Reaction time	2576	479	2820	345
Memory				
Word recognition	96.3	5.2	92.0	5.8
Reaction time	1210	200	1328	148

ner (Shimadzu-Marconi Magnex Eclipse, Kyoto, Japan). Head motions were minimized with a forehead strap and comfortable padding around the participant's head. Functional images were obtained from 25 contiguous axial slices (6 mm thick), with a 64×64 matrix and a 22-cm field of view (FOV). The repetition time (TR) was 3 s, echo time (TE) was 55 ms, and the flip angle was 90°. Before the experimental scans began, anatomical images were acquired (TR = 12 ms, TE = 4.5 ms, flip angle = 20°, pixel matrix = 256×256, and FOV = 25.6×25.6 cm). Participants practiced behavioral tasks with some pieces of instruction during the collection of anatomical images. The stimuli generated from the software Presentation (Neurobehavioral Systems Inc., San Francisco, CA, USA) were synchronized with the scanner sequence. Participants could view the stimuli on a projected screen via a mirror in the head coil tilted at 45°.

fMRI data analysis

Activation areas

We identified activation areas related to three task conditions for each participant. Off-line analyses were performed on a Dell computer by SPM99 (Wellcome Department of Cognitive Neurology, London, UK) implemented in MATLAB (MathWorks Inc., Sherborn, MA, USA). Five initial images of each scan were discarded from the analysis to eliminate non-equilibrium effects of magnetization, and the remaining 258 volumes of functional images were used for the subsequent analysis. All the functional images were realigned to correct for head movement, and we selected the images with less than 1-mm movement within each scan. The lack of data from one participant was analyzed further because the data did not meet the criterion, leaving 10 participants for each span group. Following realignment of the functional images, the anatomical image was coregistered to the mean

Table 2
Activation areas under Arithmetic + Memory, Arithmetic, and Memory conditions for high- and low-span groups

Brain region	Brodmann area	Arithmetic + Memory					Arithmetic					Memory				
		x	*y*	*z*	*Z* score	voxels	*x*	*y*	*z*	*Z* score	voxels	*x*	*y*	*z*	*Z* score	voxels
High-span group																
anterior cingulate cortex	LR32	−8	20	40	6.19	25	4	24	36	5.15	4					
prefrontal cortex	L46	−44	38	8	6.10	18	−44	38	8	5.09	3					
inferior frontal cortex	L44/9	−46	10	28	6.55	125	−46	10	26	6.14	103					
		−52	24	24	5.78		−54	12	22	5.94						
superior parietal lobule	L7	−24	−56	46	7.16	470	−28	−64	52	6.94	557					
		−40	−38	48	6.13	88	−44	−36	44	6.41	168					
	R7	32	−58	50	7.42	425	30	−62	50	7.15	331					
inferior temporal cortex	L37						−50	−62	−2	5.92	52					
	R37	42	−58	−12	6.10	55										
visual association cortex	L18/19	−30	−78	18	7.53	2253	−22	−82	−12	7.13	507	−16	−94	2	7.25	142
							−26	−90	14	6.57	402					
	R18/19	42	−66	−6	6.00		22	−82	−14	7.18	1690	34	−92	4	6.23	85
												14	−94	0	5.75	39
cerebellum	R	24	−78	−46	5.75	35	20	−78	−46	6.61	68					
Low-span group																
anterior cingulate cortex	L32	−6	22	42	5.58	23	−10	24	42	5.67	74	−4	18	50	5.84	87
prefrontal cortex	L46	−46	36	10	4.98	6	−42	32	14	5.03	2					
inferior frontal cortex	L44/9	−48	10	28	6.04	139	−50	12	24	6.02	108					
		−38	16	24	5.19											
premotor cortex	L6	−30	6	52	6.26	47	−30	6	50	6.72	118					
superior parietal lobule	L7	−24	−54	52	6.88	1515	−22	−54	50	7.12	1570					
	R7	28	−54	46	5.94		28	−58	50	6.03						
inferior temporal cortex	L37						−50	−56	−8	5.66	34					
visual association cortex	L18/19	−30	−84	18	6.58		−14	−92	−4	6.78		−16	−98	−2	6.31	170
	R18/19	30	−84	−2	7.14	1694	14	−84	6	6.82	1476	22	−94	4	6.35	216
cerebellum	L	−4	−78	−20	6.91		−2	−62	−22	5.76	140					
	R	4	−74	−16	7.04	607	8	−76	−20	6.72	278					

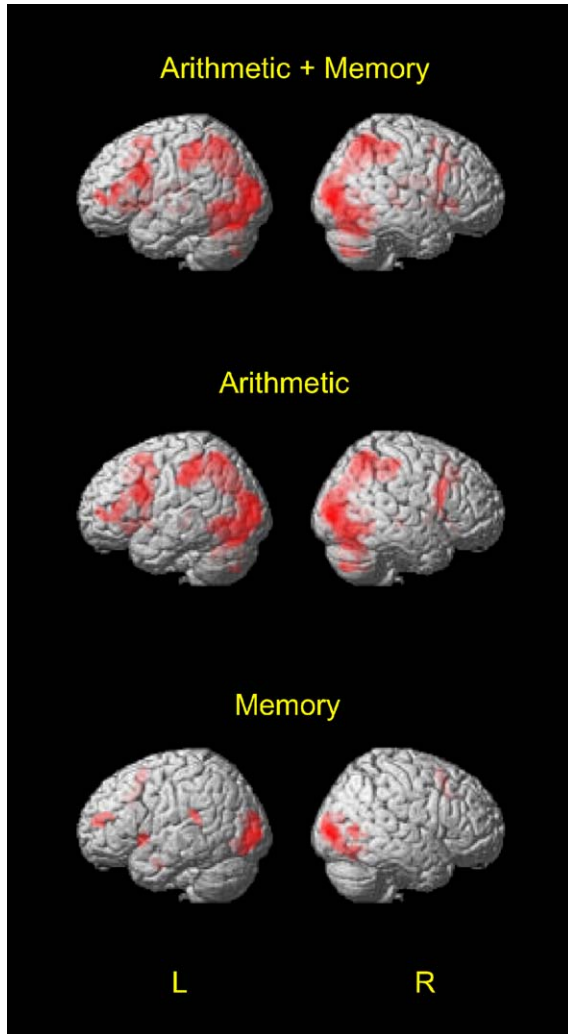*Note:* The threshold for significant activation is corrected $P < 0.05$ at voxel level.

Fig. 2. Averaged activation areas in high-span group under three task conditions. The threshold for significant activations is corrected *P* < 0.05 at the cluster level.

functional image. These functional images were normalized by the anatomical image, then spatially smoothed with an isotropic Gaussian filter (6-mm full-width at half-maximum).

We performed several statistical adjustments at this stage of the analysis. The box-car function was used to identify voxels related to the task paradigm, baseline drifts were cut off using a high-pass filter with maximal frequency of task alternation period (384 s), and a hemodynamic response function was applied as a low-pass filter. A random-effects model for SPM99 was used to obtain averaged activation data for the high- and low-span groups. Referring to the brain atlas of Talairach and Tournoux (1988), we specified activation areas of each task condition at the threshold *P* < 0.05, corrected for multiple comparison.

Signal intensity

We estimated the mean percentages of signal changes across each task condition for each participant to compare signal intensity between the high- and low-span groups. On the basis of the activation areas derived from group data, the ACC (Brodmann area: BA 32), left PFC (BA 46), left IFC (BA 44/9), and left SPL (BA 7) were anatomically determined as ROIs per task condition and participant. As briefly discussed earlier, previous studies demonstrated that the ACC and left PFC are associated with central executive functioning for task management (Bunge et al., 2000; D'Esposito et al., 1995; Smith and Jonides, 1999) and that the left IFC and left SPL play predominant roles in verbal and arithmetic cognitive abilities, respectively (Awh et al., 1996; Chochon et al., 1999; Poldrack et al., 1999; Rickard et al., 2000).

Time-series fMRI data of local maxima in the ROIs were computed under the Arithmetic + Memory, Arithmetic, and Memory conditions for each participant. Averaged signal changes of the baseline epochs were subtracted from those of each task condition, although the first images within each task epoch were excluded to discount the hemodynamic response lag. We obtained the mean signal intensity of the three task conditions for the high- and low-span groups in each ROI.

An individual-based regression analysis was administered to further examine the relationship between task performance and signal intensity. The regression analysis can confirm whether signal intensity of ROIs shows a positive or negative correlation with task performance (Bunge et al., 2001). Signal changes for each participant were computed as a function of accuracy in word recognition under the Arithmetic + Memory and Memory conditions and accuracy on arithmetic verification under the Arithmetic condition.
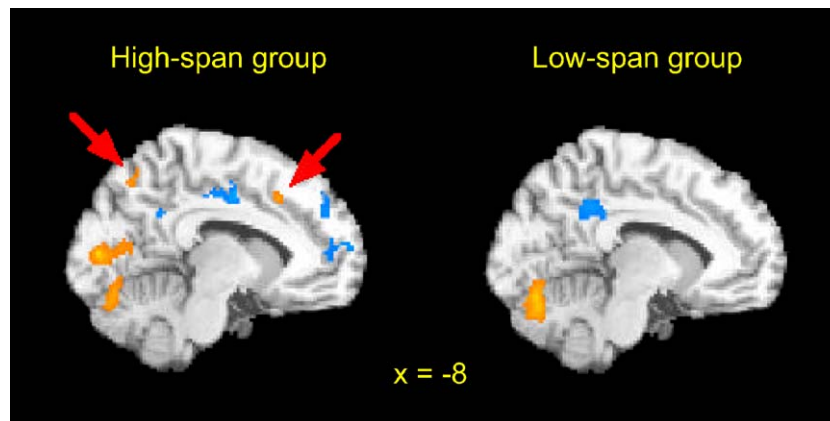

Fig. 3. Activation areas (orange) and deactivation areas (blue) derived from dual-task minus single-task conditions at the threshold of uncorrected *P* < 0.001. Arrows indicate activations of the ACC and precuneus.

Structural equation modeling

We used SEM to construct path models for the high- and low-span groups and to specify the best fitting models that can account for time-series fMRI data in all the ROIs. The structural models were computed by minimizing the difference between observed and predicted covariances of the fMRI data; the parameters in the structural models were represented as path coefficients, corresponding to an estimate of effective connectivity between the ROIs (Büchel and Friston, 1997; Horwitz et al., 1999).

We followed the SEM procedure used by Bullmore et al. (2000). First, 258 volumes of fMRI data of local maxima in each ROI were standardized to zero mean and unit variance for each participant. We adopted the data derived from the Arithmetic + Memory condition because performance differed between the high- and low-span groups. Second, an average pattern of time-series signal changes for the two span groups was identified by principal component analysis. Factor loadings of the first principal component in each time-point were estimated using the standardized data for each participant and were defined as measure of central tendency for each span group.

Finally, based on the time-series factor loadings, path models were computed by a maximum likelihood method with the software SPSS 10.0J and Amos 4.0J (SPSS Japan Inc., Tokyo, Japan). Following the recommendation by Hu and Bentler (1998), we selected several fit indices to assess the path models: the χ^2 statistics, standardized root-mean-square residual (SRMR), and comparative fit index (CFI), determining that non-significant χ^2 statistics represent a good fit. SRMR values less than 0.05 and CFI values above 0.95 generally indicate a better fit.

Results

Behavioral results

Table 1 shows performance of high- and low-span groups for each task condition. As expected, accuracy in word recognition was better in the high-span group than in the low-span group under the Arithmetic + Memory condition, but not under the Memory condition. However, mean RTs of word recognition did not differ between the two span groups. We did not find significant performance differences in arithmetic verification between the high- and low-span group; accuracy for all the participants exceeded 70% and all responses were given within 4 s. The results from an analysis of variance (ANOVA) including variables of span groups and task conditions are described below.

A 2 (high-span vs. low-span) × 2 (Arithmetic + Memory vs. Memory) ANOVA on accuracy of word recognition demonstrated that main effects for span groups and task conditions were significant [$F(1,18) = 19.94$, $P < 0.001$; $F(1,18) = 21.04$, $P < 0.001$, respectively]. The interaction was also significant [$F(1,18) = 14.49$,
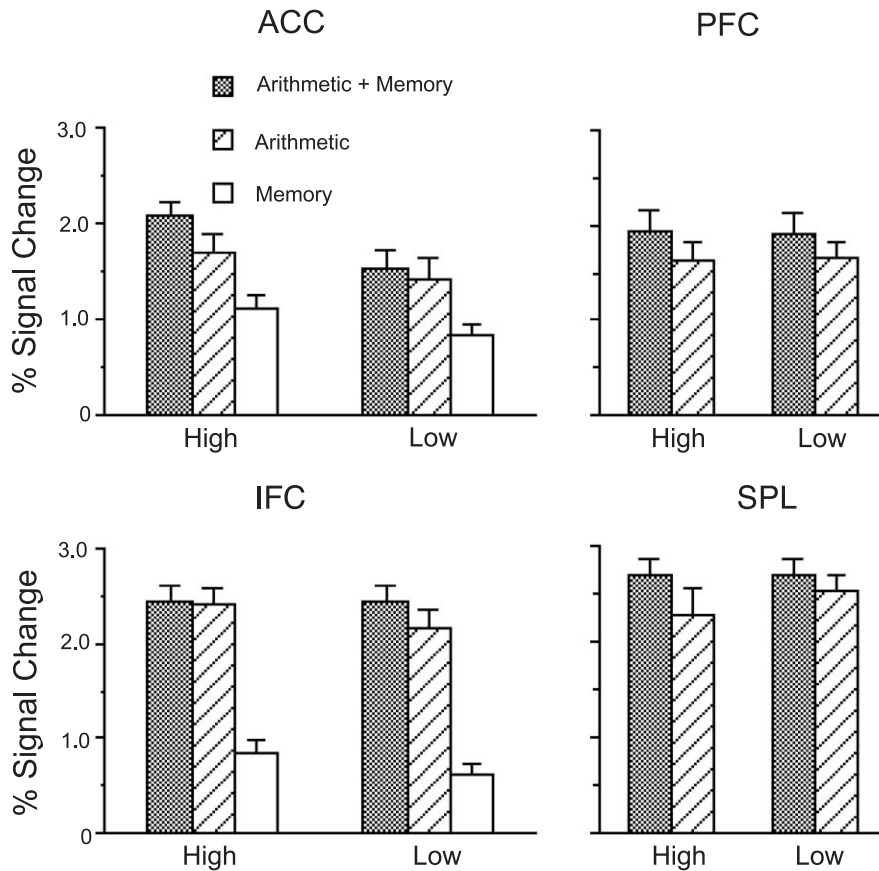

Fig. 4. The mean percentage of signal changes in the ACC, left PFC, left IFC, and left SPL is depicted across each span group for each task condition. Error bars represent standard error of the means.

$P < 0.01$]. Mean RTs on word recognition were faster under the Memory condition (1269 ms) than under the Arithmetic + Memory condition (1385 ms) [$F(1,18) = 36.81$, $P < 0.001$], although the main effect of span groups and interaction were not significant.

A 2 (high-span vs. low-span) × 2 (Arithmetic + Memory vs. Arithmetic) ANOVA of accuracy of arithmetic verification demonstrated that the main effect on span groups was marginally significant [$F(1,18) = 3.29$, $P < 0.10$], although the main effect on task conditions and the interaction were not significant. Mean RTs were

faster under the Arithmetic + Memory condition (2589 ms) than under the Arithmetic condition (2698 ms) [$F(1,18) = 10.11$, $P < 0.01$], although the main effect of span and interaction did not reach significant level.

Under the baseline condition, there was not a significant difference of mean RTs for arrow discrimination: 787 ms for the high-span group and 839 ms for the low-span group. Thus, it was unlikely that simple visuomotor ability differed between the two span groups.
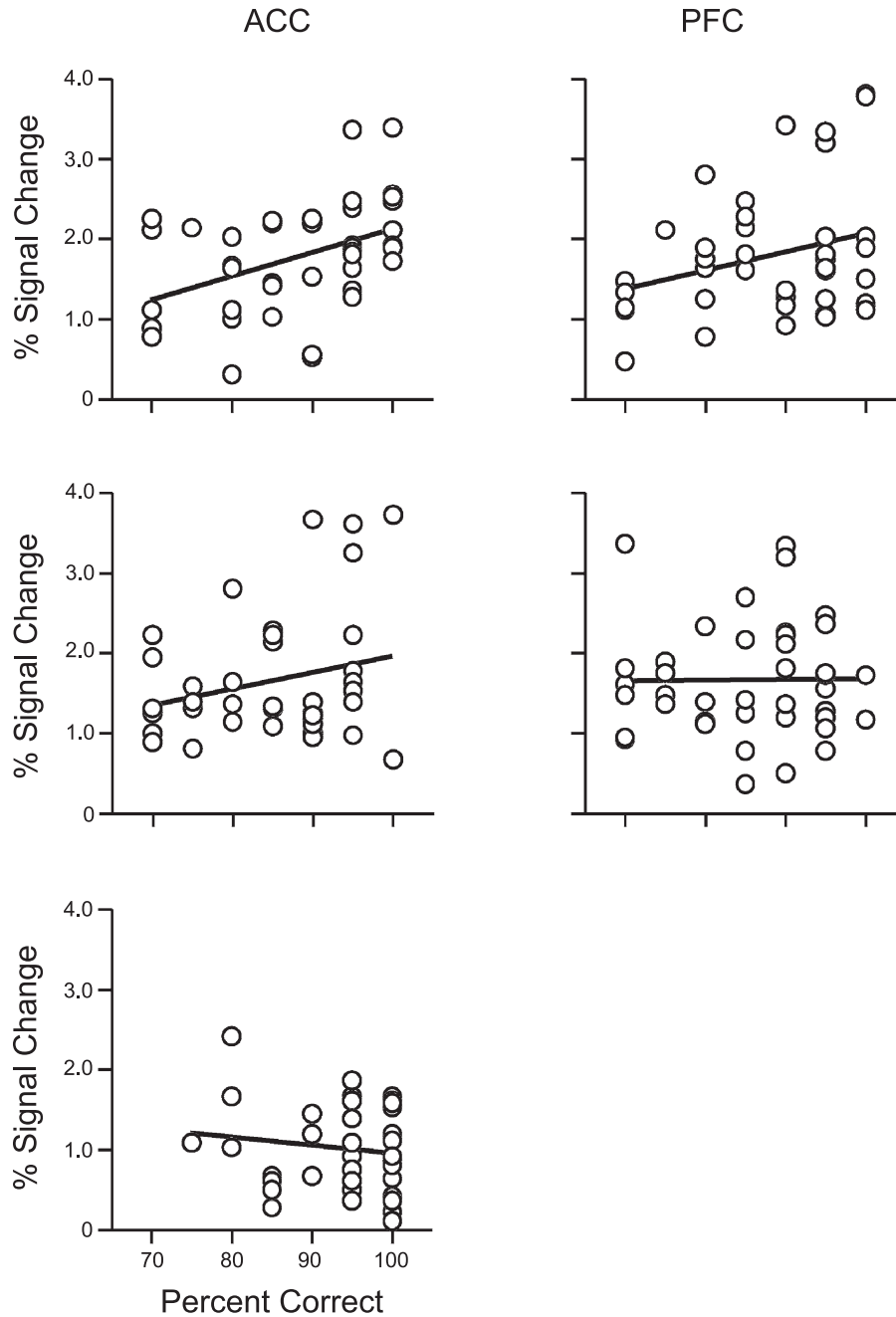

Fig. 5. Scatter plots for correlations between signal intensity and task performance in the ACC and left PFC. Top, middle, and bottom panels correspond to Arithmetic + Memory, Arithmetic, and Memory conditions, respectively.

fMRI results

Activation areas

Table 2 shows activation areas per span group and task condition above a threshold of corrected $P < 0.05$. We performed between-subjects t tests to compare activation areas between the two span groups, but no significant area survived for any task condition. The results indicated that brain activations of the high- and low-span groups overlapped considerably (Fig. 2). We administered within-subject t tests to make a comparison of activations under the Arithmetic + Memory condition and the average activation of Arithmetic and Memory conditions. The ACC ($x, y, z = -8, 20, 40$, and $Z = 4.88$) and precuneus ($x, y, z = -8, -66, 52$, and $Z = 4.80$) were recruited in the high-span group, but not in the low-span group, when the threshold of uncorrected $P < 0.001$ was used (Fig. 3). For both span groups, the left IFC, bilateral SPL, and bilateral visual association cortex were activated, while the posterior cingulate cortex (BA 31) and bilateral superior temporal cortex (BA 22) were deactivated.

Cortical activations were found in the ACC, left PFC, left IFC, bilateral parietal lobe, and bilateral visual association cortex under the Arithmetic + Memory and Arithmetic conditions. Under the Memory condition, however, activations of the bilateral visual association cortex were only observed in the high-span group, whereas the ACC and bilateral visual association cortex were activated in the low-span group. Additional areas were recruited

when a cluster-level threshold of corrected $P < 0.05$ was used (Fig. 2; bottom). Local maxima were located in the ACC ($x, y, z = -10, 20, 38$, and $Z = 4.38$), left PFC ($x, y, z = -32, 42, 20$, and $Z = 4.74$), and left IFC ($x, y, z = -46, 12, 6$, and $Z = 4.08$) for the high-span group, while local maxima were located in the left IFC ($x, y, z = -44, 14, 4$, and $Z = 4.43$) for the low-span group. Distances of local maxima between Arithmetic and Memory conditions were separated by 20.1 mm for the high-span group and 21.0 mm for the low-span group, although the left IFC was activated under for all the task conditions. The results indicated that local maxima were lower under the Memory condition than under the Arithmetic condition.

Signal intensity

Fig. 4 shows the mean percentage of signal changes in each ROI across each task condition for each span group. Under the Memory condition, the left PFC and left SPL were excluded so that we found only significant activations of the ACC and left IFC. It was in the ACC that the mean percentage of signal changes for the high-span group was greater than that for the low-span group under the dual-task condition, but not under the single-task conditions, indicating that the results derived from signal intensity were consistent with behavioral interaction between span groups and task conditions. We found that the signal changes in the left PFC were higher under the Arithmetic + Memory condition than under the Arithmetic condition, and that the signal changes in the ACC and left IFC were greater under

Top-down model
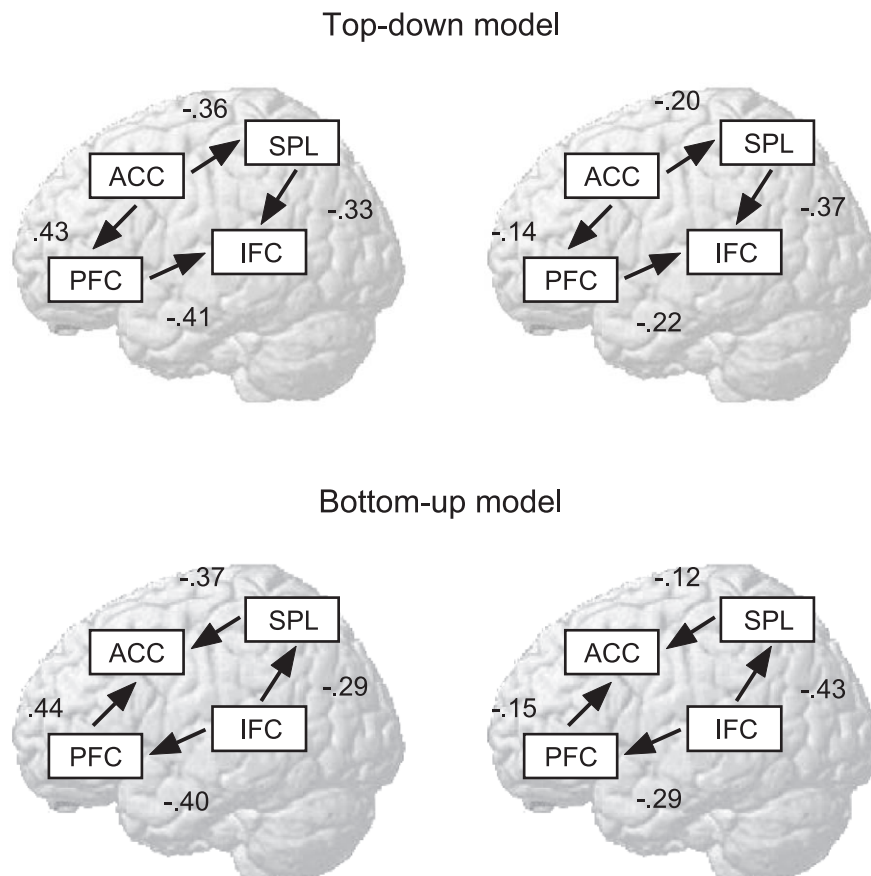

Bottom-up model

Fig. 6. Two path models for high-span group (left column) and low-span group (right column). All the path coefficients in the models are significant ($P < 0.05$). ACC: anterior cingulate cortex, PFC: left prefrontal cortex, IFC: left inferior frontal cortex, SPL: left superior parietal lobule.

the Arithmetic + Memory condition than under the Memory condition. The results from an ANOVA, including variables of the span groups and task conditions, are described below.

In the ACC, a mixed-design 2 × 3 ANOVA demonstrated that the main effects for span groups and task conditions were significant [$F(1,38) = 7.42$, $P < 0.01$; $F(2,76) = 12.51$, $P < 0.001$], although interaction did not reach a significant level. Post-hoc analyses indicated that the signal changes were greater for the high-span group (2.09%) than for the low-span group (1.52%) under the Arithmetic + Memory condition, but not under the Arithmetic condition (1.68% and 1.42%, respectively) and the Memory condition (1.12% and 0.82%, respectively). The signal changes were greater under either the Arithmetic + Memory condition (1.80%) or Arithmetic condition (1.55%) than under the Memory condition (0.97%). In the left PFC, a 2 × 2 ANOVA demonstrated that the main effect of task condition was significant [$F(1,38) = 5.13$, $P < 0.05$], although neither the main effect of span groups nor interaction was significant. The signal changes were higher under the Arithmetic + Memory condition (1.92%) than under the Arithmetic condition (1.64%). In the left IFC, a 2 × 3 ANOVA demonstrated that the main effect of the task conditions was significant [$F(2,76) = 112.93$, $P < 0.001$], although neither the main effect of the span groups nor interaction were significant. The signal changes were greater under either the Arithmetic + Memory condition (2.44%) or Arithmetic condition (2.28%) than under the Memory condition (0.73%). In the left SPL, a 2 × 2 ANOVA demonstrated that the main effects and interaction did not reach significance.

Referring to Bunge et al. (2001), we performed an individual-based regression analysis to compute brain-behavior correlations. We focused on signal intensity in the ACC and left PFC because significant differences of span group and task condition emerged. Fig. 5 represents plotted data of each participant. Under the Arithmetic + Memory condition, we found that correlation in the ACC was significant [$r(38) = 0.43$, $P < 0.01$], although correlation in the left PFC was marginally significant [$r(38) = 0.29$, $P < 0.10$]. These results indicated that the signal intensity increased with higher accuracy in word recognition and arithmetic verification. However, correlation in the ACC and PFC did not reach a significant level under the Arithmetic condition [$r(38) = 0.24$ and 0.01, respectively], while correlation in the ACC was not significant under the Memory condition [$r(38) = 0.14$]. The results indicated that the signal intensity of the ACC was correlated with dual-task performance, rather than single-task performance.

Structural equation modeling

We constructed path models including the ACC, left PFC, left IFC, and left SPL for the high- and low-span groups. As highlighted by Büchel and Friston (1997), it is important to identify the underlying anatomical model when SEM is applied to neuroimaging data. Devinsky et al. (1995) reported that the ACC is associated with the PFC, orbitofrontal cortex, anterior insula, supplementary motor cortex, premotor cortex, and posterior cingulate cortex. The ACC is also connected to the SPL via the posterior cingulate cortex, but there is no direct connection between the ACC and IFC. The PFC is adjacent to the IFC, which is associated with the SPL via an angular gyrus. It is reasonable to assume that the ACC and IFC are connected to the PFC and SPL, and consequently 16 ($=2^4$) types of path models were obtained in terms of combinations of arrow directions and ROI connections.

Table 3
Fit indices of top-down and bottom-up models for high- and low-span groups

Model	df	χ^2	P	SRMR	CFI
High-span group					
Top-down	2	4.04	0.133	0.035	0.989
Bottom-up	2	13.41	0.001	0.069	0.937
Low-span group					
Top-down	2	5.20	0.074	0.046	0.963
Bottom-up	2	6.21	0.045	0.055	0.951

Fig. 6 shows two representative models. The top-down and bottom-up models assume that the ACC and left IFC are an executive controller, respectively, by which functions of other brain regions are affected. The top-down model was better fit than the bottom-up model for both span groups from the perspective of indices (Table 3). The major difference in the two top-down models involved path coefficients from the ACC to the left PFC, which indicated positive for the high-span group (0.43) and negative for the low-span group (−0.14). A 95% confidence interval of the path coefficients ranged from 0.30 to 0.53 for the high-span group and from −0.03 to −0.24 for the low-span group. The results suggest that activities in the ACC are closely related to those in the left PFC in the high-span group.

Discussion

The main goal of the present study was to compare several aspects of brain activities in the high-span group with those in the low-span group under dual-task and single-task conditions. Under the dual-task condition, central executive functioning for frequent shifting of attention was required to alternate word retention with arithmetic verification. We initially employed a behavioral study to obtain participants' span scores on the working memory task, then divided the candidates into the high- and low-span groups for an fMRI study. In the fMRI experiment, all the participants performed word retention and arithmetic verification concurrently or separately. The behavioral results showed that performance was better for the high-span group than for the low-span group under the dual-task condition, but not under the single-task conditions. The fMRI results indicated that brain activities in the ACC and left PFC were primarily related to the differences of span group and task condition. This section can be summarized as follows. First, we identified the relationship between brain activations and cognitive processes in each task condition. Next, we discussed the causes leading to group differences from the view of effective connectivity in structural models and signal intensity in the ROIs. Finally, we examined whether there was a specific brain activity related to the dual-task performance by comparison between the dual-task and single-task conditions.

Task-related activations

It was only under the Arithmetic + Memory condition that group difference in accuracy on word recognition was observed, indicating that working memory performance depends on executive function for shifting of attention, rather than cognitive functions for two component tasks: word retention and arithmetic verification. The behavioral results were consistent with the proposal by

Engle et al. (1999), in which the executive function for regulating concurrent cognitive processes made a large contribution to higher level cognition such as reading comprehension and general fluid intelligence. More importantly, the fMRI results indicated that signal changes for the high-span group were greater than those for the low-span group in the ACC, but not in other ROIs. Taking these findings into account, it is suggested that the ACC plays an important role in task management under demanding dual-task situations (Bush et al., 2000; D'Esposito et al., 1995; Duncan and Owen, 2000; Smith and Jonides, 1999).

Previous studies have often emphasized that the ACC showed greater activation when confronted with response conflict such as a Stroop task (Bush et al., 1998; MacDonald et al., 2000). However, although activations of the ACC were observed under all task conditions in the present study, explicit prepotent responses were not included, even under the dual-task condition. It was suggested that activations of the ACC reflected central executive functioning for shifting of attention between word retention and arithmetic verification, rather than the resolution of cognitive conflict.

The possibility may exist that the activation of the ACC was derived from individual differences of mental effort or strategy (Raichle, 1993). The fact that a set size of five items makes working memory tasks challenging even to normal observers is well known (Engle et al., 1999; Smith et al., 2001; Turner and Engle, 1989). However, it was unlikely that poor performers failed in their efforts to perform the operation span task because accuracy of all the participants on word recognition and arithmetic verification exceeded 70%. It was unlikely that participants used an idiosyncratic strategy for retention of target words because they were instructed to retain the words by rote rehearsal. We believed that the effects of mental effort and strategy were minimized by screening of participants, careful instruction in the behavioral tasks, and estimation of averaged data for each span group.

Under the Arithmetic condition, mean accuracy on arithmetic verification was relatively high (above 80%) for each span group, and it took approximately 3 s to judge whether arithmetic problems were correct. It is argued that verification of simple arithmetic such as $5 + 3 = 8$ and $2 \times 6 = 12$ is faster (around 1 s) than verification of complex arithmetic because the retrieval of basic arithmetic facts from long-term memory has been overlearned (Ashcraft, 1995; Faust et al., 1996; Rickard et al., 2000). Our results indicated that arithmetic problems such as $(3.5 \times 2) + 1 = 8$ required not only retrieval of arithmetic facts, but also manipulation of interim products, thus several calculation steps were involved. The fMRI results showed that activations were primarily observed in the left PFC, left IFC, and bilateral parietal lobe. Previous studies have often demonstrated that a neural network between the frontal lobe and parietal lobe plays an important role in several arithmetic abilities. The sense of numerical quantity and the magnitude comparison of two numbers are associated with the parietal lobe, particularly in the left hemisphere, although the retrieval of arithmetic facts and arithmetic procedure involves the left IFC (Chochon et al., 1999; Dehaene et al., 1999; Rickard et al., 2000). Manipulation of information in complex arithmetic is mediated by the PFC (Dehaene et al., 1999; Zago et al., 2001). These findings supported the results of the present study in which complex arithmetic activated diverse brain regions.

It appears that the activation of the left PFC under the Arithmetic + Memory condition was strongly associated with manipulation of representations for arithmetic verification because the brain region was activated under the Arithmetic condition but not under the Memory condition. However, the results also demonstrated that the mean percentage of signal changes was higher under the Arithmetic + Memory condition than under the Arithmetic condition, suggesting that the left PFC was activated by additional mental processes with the exception of arithmetic verification. Rypma et al. (1999) highlighted the possibility that the PFC is activated to a greater extent when the requirement of the working memory task exceeds the capacity of short-term memory in the left IFC. Bunge et al. (2000) also found that the signal changes of the PFC were larger under the processing-and-storage condition than under the storage-oriented condition, using the reading span task. On the basis of a large body of empirical evidence, Cowan (2001) argued that pure short-term memory capacity involves three to four items. These findings indicate that the PFC is related to not only the manipulation of representations within the working memory, but also strategic control for enhancement of working memory capacity. We suggest that the activation of the left PFC under the Arithmetic + Memory condition was recruited by strategic control (e.g., chunking) for retention of target words as well as manipulation of interim products in arithmetic verification.

Under the Memory condition, the mean accuracy of word recognition exceeded 90% and did not differ between the high- and low-span groups. The behavioral results indicated that all the participants could concentrate on word maintenance, and consequently an individual difference in performance did not emerge. The activation pattern of the left IFC and ACC was consistent with the findings of Awh et al. (1996) that Broca's area and the ACC were activated during delayed recognition of letters, and with the idea that activations in the left IFC reflect subvocal rehearsal of words or letters based on a verbal working memory subsystem: the phonological loop (Paulesu et al., 1993; Poldrack et al., 1999; Rypma et al., 1999).

Rickard et al. (2000) argued that the activation of the IFC was linked with syntactic processing to understand arithmetic problems themselves. Local maxima of the Arithmetic + Memory condition were near those of the Arithmetic condition, although the left IFC was activated under both the Arithmetic and Memory conditions. Signal changes under the Arithmetic + Memory and Arithmetic conditions outperformed those under the Memory condition. It was suggested that cognitive functions for word retention and arithmetic verification were separately localized within the left IFC, and that the activation of left IFC under the Arithmetic + Memory condition was attributed to retrieval of arithmetic procedures rather than retention of target words.

Effective connectivity for high- and low-span groups

The path model in which the ACC was characterized as an attentional controller for top-down processing provided the best fit for both the high- and low-span groups. The results indicated that the functions of task-dependent brain regions (i.e., the left IFC and left SPL) were either directly or indirectly influenced by the activation of the ACC. The significant difference between the path models of the two span groups was clearly described as an estimate of effective connectivity from the ACC to the left PFC. The path coefficient was positive for the high-span group (0.43) and negative for the low-span group (−0.14), suggesting that closer cooperation between the ACC and left PFC was associated with enhancement of dual-task performance. Büchel et al. (1999) found that changes in effective connectivity indicated plasticity of inter-region functional

network. They tested the hypothesis that an estimate of the effective connectivity between task-related activation areas increases with behavioral learning, focusing on the connection between dorsal and ventral pathways during object-location learning task so that functions of location memory and object identification are responsible for the parietal cortex and inferior temporal cortex, respectively. The results showed that the estimate of effective connectivity between the two brain regions became larger as participants gained more practice. Consistent with the findings, the present study demonstrates that estimate of effective connectivity between the ACC and left PFC plays a critical role in predicting working memory performance, beyond the level of cognitive processes.

It has recently been argued that the ACC and PFC are associated with general fluid intelligence and executive control. Duncan et al. (2000) suggested that general fluid intelligence of a common function for spatial and verbal cognitive abilities was based on a specific frontal network including the ACC and PFC, although their data were not sufficient to show it. Gray et al. (2003) further examined the relationship between general intelligence and attentional control, using the Raven's Advanced Progressive Matrices and *n*-back task to clarify whether general intelligence is supported by attentional control. The results demonstrated that general intelligence related to reasoning was positively correlated with high-interference trial of the *n*-back task, in which the ACC and PFC were activated. Osaka et al. (2003) showed that the correlation coefficient between the ACC and left PFC was greater for good performers than for poor performers during the listening span task. The operation span task includes central executive functioning for attention shifting because word retention and arithmetic verification are independent (Miyake et al., 2000; Smith et al., 2001), while the listening span task requires executive control for inhibition of irrelevant information because word retention and sentence verification are interdependent (Osaka et al., 2003). The present study indicates that brain activities in the PFC are controlled by those in the ACC under task-switching processes, suggesting that domain-general characteristics of the central executive are supported by synchronization of activation in the two brain regions.

Consider here why the cooperation between the two brain regions is a crucial factor for individual differences in working memory performance. We argued that the activation of the ACC was related to central executive functioning for attention shifting, although the activation of the PFC was associated with both manipulation of interim products in arithmetic verification and strategic control for retention of target words. The results indicated that the ACC and PFC supported the higher cognitive processes, rather than lower cognitive processes such as retrieval of arithmetic procedure or rote rehearsal for word retention. Neuroimaging studies have suggested that the ACC is involved in the online monitoring of task performance (Bush et al., 2000; Carter et al., 1998; D'Esposito et al., 1995). Consistent with those findings, we demonstrated that the top-down model accounted for time-series fMRI data in all ROIs more appropriately than the bottom-up model. It is reasonable to assume that predictive power of working memory performance is primarily responsible for central executive functioning based on a distributed neural network consisting of the ACC and PFC.

Similarities existed between coefficients of the path models for each span group. For example, path coefficients from the left SPL to the left IFC were negative for both the high-span group (−0.33) and low-span group (−0.37). It was interpreted that signal changes of the left IFC associated with retrieval of arithmetic facts and/or rehearsal of target words were suppressed when signal changes of the left SPL linked with judgment of arithmetic problems were enhanced. The findings suggested that increases in time-series signal changes in one brain region are not always synchronized with those in other brain regions during a working memory task.

Signal intensity for high-span and low-span groups

We found that signal intensity in the ACC was higher for the high-span group than for the low-span group under the dual-task condition, but not under the single-task conditions. The pattern of the fMRI results corresponded to that of the behavioral results. However, there may be some doubt that signal changes are greater for the low-span group than for the high-span group, because poor performers are relatively more sensitive to cognitive demands of the operation span task than good performers.

Smith et al. (2001) demonstrated that signal intensity in the left PFC was greater in poor performers than in good performers, using the operation span task. They also found that signal intensity in the ACC was higher in good performers than in poor performers, but they did not draw conclusions from the findings. We did not find a specific brain region in which the signal changes in the high-span group were smaller than those in the low-span group, a possible reason being that the recognition procedure differed between the previous and present studies. In the study by Smith et al. (2001), participants were asked only to judge whether a probe list of five words was identical to the target words at the end of the set, whereas a set of five pairs of arithmetic problems and target words was successively presented as in the present study. It was likely that good performers easily performed the operation span task because the procedure reduced the memory load of the current task. In contrast, it was suggested that the serial recognition procedure made the operation span task difficult, even for the high-span group, and consequently signal changes in the left PFC increased due to its susceptibility to memory load.

Correlations between signal intensity and task performance derived from individual-based regression analysis clearly indicated that the activation in the ACC was closely related to dual-task performance. Signal changes in the ACC showed a significant positive correlation with accuracy on word recognition under the dual-task condition, although correlations under two single-task conditions did not reach a significant level. The results from correlational data matched those from group-based data, suggesting that the signal intensity in the ACC contributed to prediction of working memory performance.

Dual-task versus single-task activations

It has been argued whether dual-task performance creates an additional activation area relative to the component tasks. In an early study, D'Esposito et al. (1995) found that a dual-task condition was associated with activations of the bilateral PFC and ACC, but not a single-task condition, suggesting that central executive functioning for task management resulted in the activation of novel areas. Recent studies, however, demonstrated that the dual-task condition created greater signal intensity of the brain regions activated under a single-task condition, rather than recruitment of new regions (Adcock et al., 2000; Bunge et al., 2000). All of these findings may be interpreted by taking the statistical threshold of activations into account. As highlighted by Henson

(2001), if cognitive processes include central executive functioning, the frontal lobe should be activated even when a single component task is performed. Unfortunately, there was not a significant difference of performance between dual-task and single-task conditions in the studies by Adcock et al. (2000) and Bunge et al. (2000). We would like to emphasize that the discrepancy of the results was caused by differences of task performance.

The pattern of activation areas differed between two span groups when we subtracted activations of single-task condition from those of dual-task condition; the ACC and precuneus were recruited into the high-span group, but not into the low-span group. For both the span groups, the left IFC, SPL, and visual association cortex were activated, although activation in the left PFC did not survive. The results were consistent with the findings by Nagahama et al. (1999) that the medial frontal lobe and precuneus were related to cognitive processes of mental set shifting during a card-sorting task. It was suggested that the activations of the ACC and precuneus reflected successful and efficient task-switching processes.

Conclusion

We emphasized the importance of the cingulo-frontal network as a reliable predictor of working memory performance. The fMRI results indicated that the ACC and left PFC were involved in central executive functioning for shifting of attention and manipulation of internal representations, respectively, during the operation span task. SEM demonstrated that activations of other ROIs were regulated by the ACC, and that closer cooperation between the ACC and left PFC was related to better task performance. We suggest that several functions of the central executive are modulated by weighting the effective connectivity between the ACC and PFC, from the perspective of the inter-region network.

Acknowledgments

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