Looking to the future: Automatic regulation of attention between current performance and future plans

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ARTICLE INFO

ABSTRACT

We investigated neuro-cognitive mechanisms involved with coordination of attention between current task performance and future action plans in prospective memory. We developed a novel task paradigm with continuous performance of a prospective memory task, where trial intervals of prospective memory targets were systematically manipulated in a periodic cycle of expanding and contracting target intervals. We found that subjects' behaviour was significantly modulated without awareness of this temporal sequence of the targets: remembering to perform a prospective memory response to target events was more successful and faster in the expanding target interval phase, at the cost of lower and slower performance of ongoing tasks, while an opposite direction of this trade-off effect was observed in the contracting target interval phase. By using functional magnetic resonance imaging (fMRI), we identified the similar trade-off effect in activations in the anterior medial prefrontal cortices (activation elevation at the target responses as well as deactivation at the ongoing responses in the expanding phase as compared with the contracting phase). The opposite direction of the trade-off was observed in the anterior cingulate cortex. These results show a clear case in which attention between current task performance and future action plans in prospective memory tasks is automatically regulated without particular task instructions or strategic control processes initiated by subjects. We suggest that medial areas of the frontal cortex specifically mediate the automatic coordination of attentional resources between current task performance and future action plans.

1. Introduction

In everyday life, we are often engaged in moment-to-moment cognitive activity in response to events occurring in the environment. At the same time, we may have a number of ideas or plans in mind that are to be realized at some time in the future. To correctly act on these delayed intentions at an appropriate time (a process that has been termed "prospective memory"; Brandimonte, Einstein, & McDaniel, 1996; Dalla Barba, 1989; Meacham & Singer, 1977), our cognitive resources are thought to be regulated between performance of whatever task we are currently engaged in and thoughts about our future plans. This kind of regulatory process between attention towards current and future behaviours has been a matter of debate in studies of prospective memory. Specifically, it has been controversial exactly how anticipatory thoughts about our future plans interfere with the performance of an ongoing task (e.g., McDaniel & Einstein, 2000), or how such a behavioural interaction may be reflected in patterns of brain activity.

Cognitive models of prospective memory suggest a number of possible ways in which attention may be coordinated between current and intended actions. For example, McDaniel and Einstein (2000) describe a multi-process framework in which attentional resources can be strategically allocated towards monitoring the environment for the target event signaling that a delayed intention should be performed, or in which anticipated environmental conditions can be used to automatically reinstate the intended action on encountering the target event. Echoing the first of these possibilities, Smith and Bayen (2004) have proposed that capacity-consuming preparatory attentional processes are used during performance of a current (ongoing) task to monitor for the occurrence of the target event. Consistent with this view, Smith (2003) found that addition of a delayed intention came at a cost to ongoing performance, reflected in longer reaction times for the ongoing task. Similarly, Marsh, Hicks, Cook, Hansen, and Pallos

(2003) found that the effect of a delayed intention on the performance of an ongoing task could be varied by manipulating the type of intention that had to be maintained. It is unclear, however, whether this attentional regulation necessarily occurs as a result of a conscious, controlled strategy, or can in some circumstances operate automatically and reflexively, without awareness (Marsh & Hicks, 1998; McDaniel & Einstein, 2000). Evidence from McDaniel and Einstein (1993) is consistent with the latter account, finding that participants were more likely to correctly identify and act on unfamiliar prospective memory targets (e.g., "yolif") than familiar targets (e.g., "movie"). Similarly, Cohen, West, and Craik (2001) observed that prospective memory target identification was reduced by changing the format of the target between study and test (e.g., from a word to a picture). Such evidence suggests that attentional regulation between ongoing and delayed tasks can be driven by the automatic, 'bottom-up' capturing of attention by the target event.

A number of neuroimaging studies have also examined the interplay between current processing and delayed intentions, consistently identifying an important role for anterior regions of prefrontal cortex (PFC), including Brodmann's area (BA) 10. For example, Okuda et al. (1998) reported that activity in anterior PFC during the performance of a word repetition task was greater when a delayed intention was added to the task (i.e., to respond when a specific target word appeared). Accumulating evidence suggests that distinct contributions to prospective memory may be made by lateral and medial aspects of this brain area (Burgess, Quayle, & Frith, 2001; Burgess, Scott, & Frith, 2003; Gilbert, Gollwitzer, Cohen, Oetinngen, & Burgess, 2009; Okuda et al., 2007; Simons, Schölvinck, Gilbert, Frith, & Burgess, 2006). Lateral PFC activity has been associated with maintenance of the delayed intention during performance of the ongoing task (Burgess et al., 2001; Simons et al., 2006). Conversely, medial PFC activation has been linked with detection of the prospective memory target stimulus, with deactivation observed once the target item has been identified and acted upon (Burgess et al., 2003; Simons et al., 2006).

On the basis of these findings, Burgess et al. (2003) and Simons et al. (2006) have proposed that prospective memory can be considered to involve the biasing of attention between stimulus-oriented processing required for the ongoing task and stimulus-independent processing of the delayed intention to act. According to this view, medial PFC activation during performance of the ongoing task reflects attention oriented towards the task stimuli so that satisfactory behavioural performance can be maintained, and so that the prospective memory target event can be detected when it occurs. Once the target event is identified, medial deactivation and lateral activation within anterior parts of PFC are suggested to reflect attention being disengaged from the external stimuli and oriented towards internal representations so that the relevant intention can be retrieved from memory and the specified action effected. However, the degree to which this attentional biasing occurs strategically or relatively automatically has yet to be determined.

Previous behavioural and neuroimaging studies of prospective memory have been limited because they have tended to examine the effect of a delayed intention on ongoing task performance by comparing conditions that comprise different cognitive components (either contrasting performing the ongoing task alone with performance when maintaining a delayed intention, or comparing ongoing task performance in conditions involving different delayed intentions). It can be difficult to determine from such manipulations whether differences in reaction time, accuracy, or brain activity reflect attentional allocation between the ongoing and intended actions only, or whether additional confounding processing requirements have been introduced by changing the task which could potentially affect the results (Friston et al., 1996; Sternberg,

1969). Moreover, by administering tasks to participants in separate conditions, the likelihood is increased that participants consciously decide to change their adopted strategy, potentially obscuring any role that automatic attentional regulation may play.

In the present study, we aimed to understand the relationship between performance of an ongoing task and anticipation of future behaviour by developing a paradigm in which the level of engagement in the ongoing task and in anticipation of future target responses could be varied empirically without introducing the potential confounds identified above. Participants were asked to continuously perform an ongoing cognitive task but were required to make a specific response to occasional target stimuli embedded in the ongoing trials. We manipulated the intervals between the target trials so that they decreased (a contracting target interval phase; e.g., 20, 16, and then 12 trials between target stimuli) or increased (an expanding target interval phase; e.g., 12, 16, and then 20 trials between target stimuli) systematically during the task. Pilot testing indicated that this manipulation could be achieved without participants being aware that target intervals were changing. Nonetheless, based on the assumption that the degree of target anticipation would vary with the change in the target interval, we expected that a characteristic behavioural and neurobiological trade-off would be observed between the ongoing and target responses across the contracting and expanding phases. More specifically, we predicted that target anticipation would be lower when the target stimulus appeared earlier than expected (contracting phase), resulting in a slower target response and reduced activation in medial PFC, and vice versa when the target appeared later than expected. On the other hand, speed of the ongoing response and medial PFC activity was predicted to show an opposite pattern to that of the target response, assuming that there is a trade-off between performance of the ongoing task and target anticipation.

2. Materials and methods

2.1. Subjects

Sixteen right-handed healthy volunteers (6 males and 10 females, mean age 27.8, SD 6.6 years old) participated in the study. All subjects gave written consent to participation in the study in accordance with guidelines approved by an institutional ethical committee and the Declaration of Human Rights, Helsinki 1975. None of them had a history of medical or neurological diseases.

2.2. Stimuli

Each subject underwent two separate task sessions: a dots and a number task. In both tasks stimuli were generated using Cogent2000 toolboxes (Laboratory of Neurobiology, University College London, http://www.vislab.ucl.ac.uk/Cogent/) implemented in Matlab Ver. 6.1 (The MathWorks, Inc., Natick, MA, USA) on a Windows computer, and projected on a screen behind the MRI scanner. Subjects viewed the stimuli via a mirror attached to the scanner head coil.

Stimuli in the dots task consisted of three small yellow dots, the positions of which were selected from 16 radial-circular lattice points (crossing points of 4 imaginary diagonal lines and 2 imaginary circles with radius of $1°$ and $2°$ in visual angle, Fig. 1a). A white cross-hair was presented at the center of the screen. Each stimulus consisted of either a right-sided or left-sided pattern. A right-sided pattern comprised two dots on the right side of the screen, one located at a position in the inner circle and one in the outer circle, and one dot on the left of the screen, located in the outer circle. A left-sided pattern comprised two dots located on the left of the screen and one on the right. As such, there were 128 possible patterns of dots, with the 8 patterns that constituted a collinear diagonal line including the screen center used as target stimuli (Fig. 1b). The remaining 120 non-target stimuli were pseudo-randomly arranged in a sequence so that no more than 3 right-sided or left-sided patterns were repeated in a row. Over 20 different sequences were prepared and then combined into one long sequence of more than 2500 stimuli.

In the number task, two-digit Arabic numbers from 10 to 49 and from 60 to 99 were used as stimuli. Each number was presented at the center of the screen with a non-proportional font "Courier" in white colour (Fig. 1c). Out of the 80 two-digit numbers, eight numbers that were composed of the same digit (11, 22, 33, 44, 66, 77, 88, and 99; Fig. 1d) were used as target stimuli. The 72 non-target stimuli were pseudo-randomly arranged in a sequence of about 2500 stimuli in a similar manner to the dots stimuli.
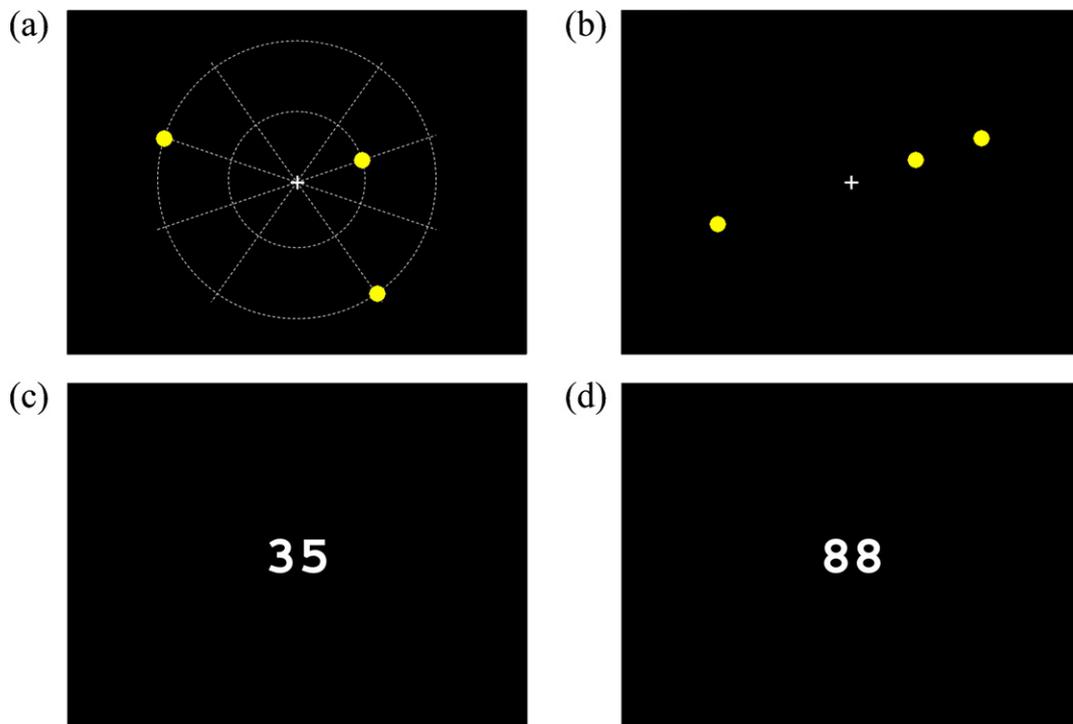
Fig. 1. Examples of stimuli in dots and number tasks. (a) Dots stimuli consisted of 3 small yellow dots that were located at crossing points of 4 imaginary diagonal lines and 2 imaginary circles (imaginary lines and circles depicted by dotted lines in the figure were not presented in the actual stimuli). A white cross-hair was presented at the center of the circle as a fixation point. Spatial configuration of the dots was either two dots in the right side of the screen and one in the left (right-sided pattern, as shown in a) or two in the left and one in the right (left-sided pattern). Each stimulus consisted of two dots located on the outer circle and one dot on the inner circle. An ongoing task for each dots stimulus was to judge whether the stimulus was right-sided or left-sided pattern by pressing corresponding buttons. There were a total of 128 patterns of the dots stimuli. (b) Eight patterns of dots that make a diagonal (radial) line pattern including the fixation cross-hair were used as target stimuli for the dots task. The subjects were required to press the third button (prospective memory response) instead of the ongoing judgment when the target stimuli were presented occasionally. (c) Number stimuli were two-digit Arabic numbers from 10 to 49 and from 60 to 99 that were presented at the center of the screen with a non-proportional font "Courier" in white colour. The subjects were required to make ongoing judgment whether each number was greater or smaller than 50 by pressing corresponding buttons. There were a total of 80 number stimuli. (d) Eight numbers that were composed of the same digit (11, 22, 33, 44, 66, 77, 88, and 99) were used as target stimuli for the number task. The subjects were required to press the third button (prospective memory response) instead of the ongoing judgment when the target stimuli were presented occasionally.

2.3. Temporal arrangement of target stimuli

For both dots and number tasks, target stimuli were embedded in the stimulus sequence based on a temporal structure of periodic expanding and contracting target intervals. In this time course, contracting and expanding target-interval phases (trial intervals between two successive targets decreased or increased, respectively) were repeated in a periodic cycle, where overall target frequency was matched between the two phases (Fig. 2). Each task lasted 20 min, in which time 15–20 repetitions of this cycle occurred, depending on the speed of each subject's response. For both tasks, the eight possible target stimuli were pseudo-randomly placed at the eight possible target positions (4 contracting and 4 expanding) in each periodic cycle so that the probability of each target stimulus at each of the 8 positions was constant.

The time-course of the target intervals in the present experiment (20-16-12-8-4-8-12-16-20-···) was determined on the basis of being optimal in terms of statistical efficiency for detecting differences in fMRI activity (i.e., sensitivity with which differential event-related responses to events of interest may be detected, given a certain amount of scanning time; Dale, 1999; Henson, 2004) and reliability of eliciting significant behavioural effects during extensive pilot testing. We conducted behavioural piloting and an fMRI model simulation study prior to the experiment, in which various target interval designs with a limited task duration were examined (15 cycles of 20-16-12-8-4-8-12-16-20-, 10 cycles of 30-24-18-12-6-12-18-24-, and so on). Behavioural effects (difference in response accuracy and reaction times across expanding and contracting phases, as shown in Section 3) tended to be more evident in the shorter target distance design than in the longer one. Moreover, the efficiency estimation was the greatest in the 20-16-12-8-4-8-12-16-20- design among various target interval designs. This observation was consistent with the previous study (Dale, 1999) showing that the statistical efficiency to detect hemodynamic response to different events improved with decreasing mean inter-event intervals
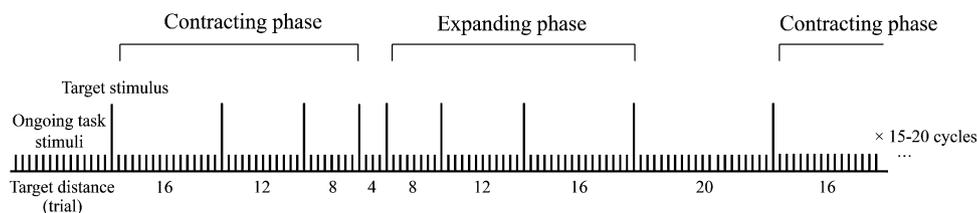

Fig. 2. A schematic illustration of the temporal structure of periodic expanding and contracting target interval task sequence. In the periodic sequence, occasional target stimuli for prospective memory response were embedded in a row of non-target stimuli for ongoing judgment in a periodical cycle of contracting and expanding target-interval phases. Trial intervals between two successive targets decreased in the contracting phase and increased in the expanding phase, where overall target frequency was matched across phases. An interval sequence of 20-16-12-8-4-8-12-16-20-··· was used in the present experiment as a behaviourally and physiologically optimal sequence according to results of pilot experiments and fMRI model simulation. This cycle of contracting and expanding phases was repeated 15–20 times, depending on speed of each subject's response, in fixed duration of 20 min for each dots and number task. For both tasks, eight possible target stimuli were pseudo-randomly placed at the eight possible target positions (4 contracting and 4 expanding) in each periodic cycle so that probability of each target stimulus at each of the 8 positions was constant. Only the data belonging to the target interval of 8, 12, and 16 were analysed since there were no data for target interval of 4 in the expanding phase and those of 20 in the contracting phase.

when the event interval was properly jittered. This condition (temporal jitter in event timings) also applied to the present experiment because the task response was subject-paced.

As for validity of fMRI modeling for sequences of rapidly presented task events, large body of theoretical and empirical studies on rapid event-related fMRI (Buckner, 1998; Buckner et al., 1998; Burock, Buckner, Woldorff, Rosen, & Dale, 1998; Dale & Buckner, 1997) have shown that fMRI signals can be accurately estimated by linear summation of temporally overlapping hemodynamic response functions elicited by multiple events of interest. Such linearity has been shown to be applied to event intervals as short as 500 ms if the event timing was temporally jittered (Burock et al., 1998). As shown in the behavioural results, reaction times for each ongoing stimulus were around 600–700 ms in our experiments, and there were no inter-stimulus intervals (subject-paced task): hence, duration of two successive target events was as long as 2–3 s at the shortest target-to-target interval (4 trials apart). Considering these temporal characteristics of the experiment (more than 2–3 s event intervals with temporal jitter), we examined the present fMRI data based on the assumption of the linear summation model. However, it should be noted that a couple of recent studies (Jung, 2009; Wager, Vazquez, Hernandez, & Noll, 2005) have indicated potential nonlinear components observed in fMRI signals especially for repetition of certain numbers (typically more than ten) of events with 1 s interval. Although these conditions do not directly apply to the present experimental design, we should keep in mind that the current results largely depend on linear components of the fMRI responses with less consideration about unknown nonlinear effects that might arise from asymmetrical time course of target events across the expanding and contracting phases.

2.4. Tasks

In the dots task, subjects performed an ongoing task in which they were asked to judge whether two dots were on the right or the left side of the screen and to press buttons with their forefinger or middle finger accordingly. If they were presented with a target stimulus (i.e., dots constituting a diagonal line pattern), they were required to press a third button with their little finger, instead of making the ongoing judgment. In the number task, subjects performed an ongoing task in which they were asked to judge whether the two-digit number was greater or smaller than 50 and to press buttons with their forefinger or middle finger accordingly. If they were presented with a target number that was composed of two of the same digit (e.g., 11, 22, etc.), they pressed a third button with their little finger. To control for the effect on brain activity of which hand was used, half the subjects were instructed to make responses with their right hand and half with their left.

The subjects performed the tasks at their own pace and each stimulus changed to the next one immediately after a response was made (no inter-trial intervals). The aim of this procedure was to minimize a chance for subjects to have conscious rehearsal of prospective memory responses during the tasks, as well as to provide statistical power for fMRI analyses. Before starting the task, subjects were instructed to make their response as quickly as possible and to concentrate primarily on the ongoing task rather than continuously watching for the prospective memory target. Subjects were instructed that if they noticed that they had responded incorrectly (e.g., making an ongoing response to a target stimulus), they could rectify their error by immediately making the correct response even if the next stimulus had already appeared. This procedure was introduced to discriminate between complete inattention/miss of the target and delayed awareness/execution of the target response. Importantly, subjects received no instructions about the expanding and contracting nature of the target intervals.

2.5. Experimental procedures

Before the fMRI acquisition, each subject undertook practice sessions comprising shortened versions of each ongoing task, receiving feedback about their performance. The order of the dots and number practice was counterbalanced across subjects, with the same order used in the fMRI experiment.

Two fMRI sessions corresponding to the two (dots and number) tasks were administered, with structural scans acquired in between. Each functional session lasted 20 min and consisted of 3 different phases: the ongoing task with prospective memory target stimuli interspersed according to the periodic schedule outlined above, a baseline task, and an instruction phase. The baseline task served as a low-level control for the periodic phase, controlling for general attention to visual stimuli and motor response, and was inserted at the beginning of the functional session and after every 5 periodic cycles. It consisted of a simple reaction time task in which left- and right-directed arrows (on the left and the right side of the screen, respectively) were alternately presented at a constant rate and the subjects followed the changes of the arrows by pressing the left or right button. The speed of the arrow's change was set to be equivalent to the mean reaction times obtained during the preceding periodic phase, and each baseline phase lasted 20 s. The subjects were instructed that this baseline task was a "finger exercise" that was to provide a brief rest during the 20-min dots or number task.

After finishing the whole experiment, subjects were asked to answer a structured questionnaire which asked about their impressions of their task performance and the temporal structure of the target intervals.

2.6. MRI measurement

Functional and structural images of the subjects' brain were acquired using a 3 T MRI scanner (Siemens Allegra, Erlangen, Germany) at the Wellcome Trust Centre for Neuroimaging, UCL. Acquisition of functional images was made by a gradient-echo echo-planar-imaging (EPI) sequence. 580 volumes of EPI images were acquired during each fMRI session. Each EPI volume consisted of 32 horizontal slices acquired in a sequential order from the top to the bottom of the entire brain. Parameters for the EPI sequence were as follows: repetition time (TR), 2080 ms; echo time (TE), 30 ms; in-plane matrix dimension, 64 by 64; sampling field of view (FOV), 192 by 192 mm^2; slice thickness, 3 mm; inter-slice gap, 1.5 mm; and flip angle, 90°. Resulting total scanning time was 1206.4 s and spatial resolution of the volume was 3 mm × 3 mm × 4.5 mm.

Acquisition of the first EPI slice was synchronised with the start of each task session. Thereafter, timing information regarding stimulus presentation, subjects' response, and each EPI scan was all recorded in the stimulus computer, and used in subsequent analyses. The first 4 volumes of the EPI were discarded from the analyses to allow for T1 equilibration. During this period, subjects were presented with a message that the finger exercise would begin shortly and to wait for the start of the task.

2.7. Image analysis

The fMRI time series were analysed with statistical parametric mapping software version SPM2 (www.fil.ion.ucl.ac.uk/spm). For each subject, the 576 EPI volumes for each session were spatially realigned to the first volume acquired, corrected for different acquisition time of each slice for each session, and spatially normalised to the standard MNI template implemented in SPM2 with an isotropic voxel dimension of 3 mm × 3 mm × 3 mm. The normalised volumes were then spatially smoothed with a three-dimensional Gaussian filter of 8 mm × 8 mm × 8 mm in full width at half maximum (FWHM).

Random effect statistical analysis was undertaken in two stages. First, EPI data for each subject were incorporated into a general linear model consisting of several block/event-related regressors convolved with a canonical hemodynamic response function, together with parameters of the subject's head-movement during each session as well as session-specific constant terms. We modeled 11 regressors of interest for each session: 2 blocked and 9 event-related. The block regressors were those modeling onset and duration of instruction and periodic phases. The event-related regressors consisted of 2 sets of 4 regressors, each modeling onsets of different trial categories in the periodic phase, and a regressor for baseline trials (simple reaction time task). The first set modeled ongoing (O) and target (T) trials for each expanding (exp) and contracting (con) period (hereafter abbreviated as Oexp, Ocon, Texp, and Tcon, respectively). To ensure that these regressors characterized the effects of expanding and contracting target intervals specifically, an additional set of regressors modeled the peripheral target intervals of each periodic phase (i.e., those with target distance of 4 and 20, which had no expanding or contracting targets, respectively).

The baseline regressor served as zero level in activation plots. To discount possible confound of different event densities between the target regressors and ongoing/baseline regressors (target trials were sparser than ongoing/baseline ones), we modeled the ongoing/baseline regressors by using only a middle trial during each block of ongoing/baseline trials (e.g., fourth trial within a block of 8 ongoing trials in-between two target trials, eighth trial within a 16-trial ongoing block, and so forth). In separate analyses, we also examined fMRI models using all trials within the ongoing/baseline blocks as the ongoing/baseline regressors, and found almost the same areas of activation clusters with the same statistical effects to the results from the middle-trial model. Therefore, we only report the data from the analyses using the middle ongoing/baseline trials here. To eliminate any confounding effects related to trial-by-trial difference in reaction times on brain activity, we also included parametric regressor modeling reaction times in each trial for each event condition.

Effects of these regressors on fMRI signal intensity changes were estimated on a voxel by voxel basis. Temporal autocorrelation of the fMRI time series was modeled out by AR(1) model. High-pass filter of around 300–400 s cut off frequency according to duration of the longest periodic cycle in each session by each subject (mean, 364 and 385 s; SD, 61 and 75 s for dots and number sessions, respectively) was applied at the model estimation. Contrast images for effects of baseline-related regressors were subtracted from those of the event-related regressors of interests (Oexp, Ocon, Texp, Tcon separately for dots and number tasks) for each subject. These contrast images were then entered into a second-level, random-effect model across 16 subjects, using a one-way analysis of variance (ANOVA) model without a constant term. Correction for non-spherically distributed error variance across conditions was applied when estimating the model (Friston et al., 2002).

To elucidate brain activations showing effects of phase and response, appropriately weighted contrasts across conditions were examined at an uncorrected threshold of $P < 0.001$ with more than 5 contiguous voxels. We also examined corrected P values in a priori regions of interest (ROIs) for prefrontal activations (i.e., medial PFCs and anterior cingulate region) to test anatomical consistency and statistical significance of the present activation results in the regions that have already been suggested to have involvement in prospective memory processes or regula-

Table 1
Performance of prospective memory and ongoing tasks.

Phase	Expand			Contract		
Target distance (trial)	8	12	16	8	12	16
Dots task						
Prospective memory						
Miss (mean %)	8.7	8.6	9.6	9.3	13.8[*]	14.1[*]
(SD)	10.7	11.5	11.9	13.4	9.9	13.9
SC (mean %)	14.1	14.3	17.5	20.9[*]	14.9	20.5
(SD)	13.9	14.1	15.3	19.1	15.3	16.5
Ongoing task						
Error (mean %)	2.2	2.0	2.2	1.7	1.5	2.1
(SD)	2.4	2.2	2.3	2.1	2.1	2.5
Number task						
Prospective memory						
Miss (mean %)	4.5	3.4	0.9	3.5	4.4	4.7[*]
(SD)	8.3	6.9	2.5	9.1	6.0	8.7
SC (mean %)	10.5	8.5	8.3	9.8	13.3[*]	12.0
(SD)	13.1	14.2	10.2	13.5	15.6	12.1
Ongoing task						
Error (mean %)	4.8	4.7	4.3	4.0	4.0	4.0
(SD)	4.5	2.2	2.7	3.0	3.0	2.5

SC: secondary correction response; SD: standard deviation.

[*] Significantly greater percentage than that of the corresponding target interval in the opposite phase (one-tailed $P < 0.05$ by a paired t-test).

tion of behavioural interference. A medial PFC ROI was drawn as 16 mm (twice as large as the spatial smoothing size applied to the fMRI data, which was the same criteria as ROI analyses in the previous study (Okuda et al., 2007) radius spheres centered at ($x = -9$, $y = 51$, $z = -9$) for the left medial prefrontal region and ($x = 12$, $y = 45$, $z = -3$) for the right medial prefrontal region, based on (de)activation peak revealed with event-based prospective memory tasks in the previous report (Okuda et al., 2007, Study 1, ongoing minus event contrast in Table 1). A ROI for the anterior cingulate region was drawn as a 16 mm radius sphere centered at ($x = 12$, $y = 18$, $z = 48$) from data reported in Morishima, Okuda, and Sakai (2010) (a region that showed involvement in reactive control of behaviour in a Stroop interference task). We used small volume correction procedure implemented in the SPM software, and examined corrected P values for family wise error in these ROIs.

3. Results

3.1. Behavioural data

Table 1 summarises error rates on the prospective memory and ongoing trials across the expanding and contracting phases. For prospective memory trials, we separately analysed the percentage of missed responses (complete failure to press the third button to target stimuli) and that of secondary corrections (making a target response immediately after erroneously making an ongoing response to a target stimulus). In most cases, mean values of miss and secondary correction rates for the targets were numerically higher in the contracting phase for both dots and number tasks, whereas error rates on the ongoing tasks showed higher mean values in the expanding phase. To statistically test effects of phase on prospective memory and ongoing performance, ANOVAs were conducted with phase (expanding, contracting) and target distance (8, 12, 16) as within-subject factors, and subjects as a random effect. There were significant (or marginally significant) effects of phase on the target miss and secondary correction rates in the dots task ($F(1,15) = 6.67$ and 3.89, $P = 0.021$ and 0.067 for miss and secondary correction, respectively). Post hoc paired t-tests comparing the data at each target distance confirmed significant differences across phases at several target distances (indicated by an asterisk in Table 1). The main effect of phase on the target miss and secondary correction rates in the number task did not reach significance ($F(1,15) = 1.51$ and 2.07, $P = 0.23$ and 0.17 for miss and secondary correction, respectively), but paired t-tests revealed significant differences across phases at several of the target distances (asterisk in Table 1). As most subjects made no or very few errors on the ongoing judgments, effects of phase on the ongoing error rates

did not reach significance ($F(1,15) = 0.82$ and 1.34, $P = 0.38$ and 0.27 for dots and number tasks, respectively). In these analyses, main effects of target distance were not significant ($F(1,15) = 1.80$ and 0.51, $P = 0.18$ and 0.61 for target miss in dots and number tasks, $F(1,15) = 1.58$ and 0.09, $P = 0.22$ and 0.91 for secondary correction in dots and number tasks, $F(1,15) = 0.53$ and 0.13, $P = 0.60$ and 0.88 for ongoing error rates in dots and number tasks, respectively). Similarly, there were no significant interactions across phase and target distance ($F(1,15) = 0.98$ and 2.54, $P = 0.39$ and 0.10 for target miss in dots and number tasks, $F(1,15) = 1.33$ and 1.53, $P = 0.28$ and 0.23 for secondary correction in dots and number tasks, $F(1,15) = 0.10$ and 0.37, $P = 0.91$ and 0.70 for ongoing error rates in dots and number tasks, respectively).

Table 2 summarises reaction times (RTs) for the prospective memory and ongoing trials. Consistent with the performance data described above, mean values for RTs of prospective memory responses were numerically higher in the contracting phase than in the expanding phase in most cases, with those of ongoing responses showing the opposite pattern (higher mean values in the expanding phase than in the contracting phase). To statistically examine phase effects on the RT data, ANOVAs were performed on the target and ongoing RTs, separately for dots and number tasks. In addition to overall mean data of the target and ongoing RTs, we also analysed the data separately for correct responses (hits) and secondary correction responses to prospective memory targets, as well as corresponding ongoing RTs before the prospective memory hit and secondary correction responses. ANOVAs revealed significant main effects of phase for all categories of data (F and P values are listed in the right most column of Table 2), except for secondary correction response to prospective memory target in the number task (marginally significant at $P = 0.085$). Paired t-tests comparing the data at each target distance confirmed significant differences across phases in most cases (indicated by an asterisk in Table 2). There were marginally significant trends in main effects of target distance for overall mean target RTs in the dots task ($F(1,15) = 3.17$, $P = 0.056$) and overall mean ongoing RTs in the number task ($F(1,15) = 3.00$, $P = 0.065$), but no other cases showed significant trends ($P > 0.15$ in all cases). As for interactions across phase and target distance, significant trends were found for hit and overall mean target RTs in the number task ($F(1,15) = 3.17$, $P = 0.056$ for both cases), but no other cases showed significant trends ($P > 0.15$ in all cases).

Table 2
Reaction times of prospective memory and ongoing responses.

| Phase	Expand			Contract			P-Value (F-Value)
Target distance (trial)	8	12	16	8	12	16	
Dots task							
Prospective memory							
Hit (mean)	771.9	763.9	773.0	794.5*	806.4*	787.6	0.004
(SD)	89.2	93.9	82.7	99.7	93.2	97.4	(11.5)
SC (mean)	889.0	895.4	934.1	1050.9*	1069.4*	1141.2*	0.017
(SD)	123.3	76.2	124.2	212.4	182.7	337.2	(8.6)
All (mean)	791.0	789.6	806.1	836.8*	847.7*	870.4*	<0.001
(SD)	92.0	85.5	87.6	93.6	83.0	107.3	(24.6)
Ongoing task							
Before PM hit (mean)	664.1	674.4*	655.7	647.8	643.7	647.8	0.003
(SD)	122.9	130.3	111.6	133.1	112.6	120.9	(13.1)
Before PM SC (mean)	640.0	607.3	614.2*	603.6	581.4	583.0	0.035
(SD)	116.8	82.7	84.0	62.7	89.6	69.7	(5.5)
All (mean)	667.5*	672.9*	660.0*	651.4	638.8	646.6	<0.001
(SD)	123.4	120.2	111.7	123.9	112.3	118.0	(29.5)
Number task							
Prospective memory							
Hit (mean)	757.3	761.9	749.2	777.1	793.4*	800.1*	0.024
(SD)	92.1	87.2	88.1	113.5	114.6	129.6	(6.3)
SC (mean)	870.6	882.1	941.2	1003.9	1073.5*	1110.9	0.085
(SD)	141.4	93.6	161.7	170.2	176.8	225.3	(3.9)
All (mean)	768.6	773.4	761.5	801.2*	831.1*	836.5*	0.001
(SD)	82.2	82.2	85.6	108.0	93.7	130.8	(16.7)
Ongoing task							
Before PM hit (mean)	727.6	724.2*	716.4*	715.7	701.8	700.7	0.001
(SD)	141.3	140.2	134.4	146.5	146.5	139.6	(19.0)
Before PM SC (mean)	652.7	694.9	715.5*	593.1	675.2	630.1	0.005
(SD)	151.2	169.8	130.1	95.9	151.3	90.2	(12.3)
All (mean)	725.6	728.3*	715.9*	713.7	701.4	696.8	<0.001
(SD)	145.6	148.8	133.6	148.5	142.1	139.2	(23.4)

Data are expressed in ms. F- and P-values show statistical data on phase effect in analyses of variance (phase (expanding, contracting) and target distance (8, 12, 16) as within-subject factors, 16 subjects as a random effect). SC: secondary correction response; SD: standard deviation; and PM: prospective memory.

* Significantly longer reaction time (one-tailed $P < 0.05$ by a paired t-test) than that of the corresponding target interval in the opposite phase.

To confirm the opposite effect of phase on target and ongoing RTs, we performed additional ANOVAs (phase (expanding, contracting) and response type (target, ongoing) as within-subject factors, 16 subjects as a random effect; collapsing across target distance) and examined the interactions between phase and response type (Fig. 3). This revealed significant interactions in each task ($F(1,15) = 48.9$, $P < 0.001$ and $F(1,15) = 25.9$, $P < 0.001$ for overall mean RTs in dots and number tasks, respectively), as well as main effects of response type ($F(1,15) = 66.6$, $P < 0.001$ and $F(1,15) = 10.9$, $P = 0.005$ for dots and number task, respectively). These effects were also significant when hits and secondary correction trials were analysed separately ($F(1,15) = 31.4$, $P < 0.001$ and
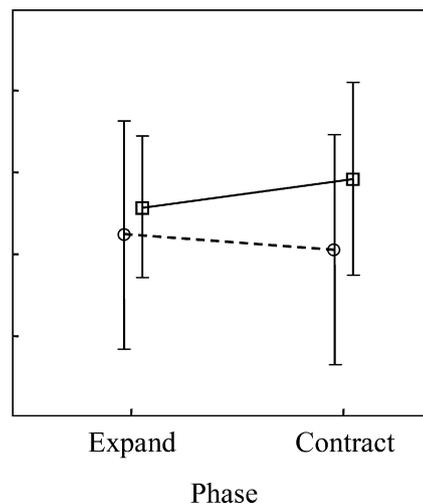
(a) Dots task
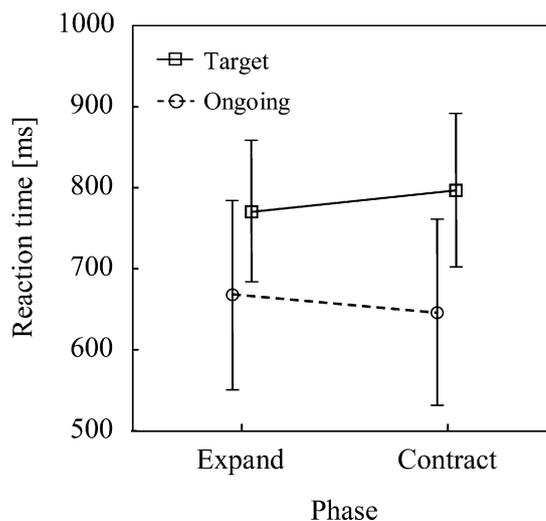
(b) Number task

Fig. 3. Mean reaction times for target (prospective memory) and ongoing responses across expanding and contracting phases in (a) dots and (b) number tasks. Significant interaction effects across response (target/ongoing) and phase (expand/contract) were found for both tasks (longer target reaction time as well as shorter ongoing reaction time in the contracting phase). Error bars show standard deviation. Data were collapsed across target intervals of 8, 12, and 16.

$F(1,15) = 12.9$, $P = 0.003$ for hit trials in dots and number tasks, respectively; $F(1,15) = 15.3$, $P = 0.002$ and $F(1,15) = 9.7$, $P = 0.011$ for secondary correction trials in dots and number tasks, respectively).

In the debriefing questionnaire after the experiment, we asked subjects whether or not they noticed any temporal structure of target appearance. Only one subject noticed any systematic variation in time-course of the target, and all subjects were surprised at being shown his/her own performance profile (i.e., reliable phase effects as described above). The one subject who noticed the target temporal structure also showed reliable phase effects. Although he reported some awareness of a temporal pattern to the task, he told us that he did not use that knowledge for any strategic preparation for the target.

3.2. fMRI data

To characterize the neurobiological correlates of the phase effect revealed in the behavioural data, we compared event-related fMRI activations across expanding and contracting phases separately for target and ongoing responses. We specifically examined brain regions showing opposite phase effects for prospective memory targets versus ongoing trials. As shown in Table 3, significantly greater target-related activation was observed in the expanding phase than in the contracting phase in the medial PFCs of both hemispheres (Fig. 4a) when data from the dots and number tasks were combined. The same regions also showed significantly greater ongoing-related activation in the contracting phase than in the expanding phase (Table 3 and Fig. 4b). To confirm these opposite phase effects, we examined interaction effects using corresponding linear contrasts across phases and responses. The same regions of bilateral medial PFC showed significant interaction effects (Table 3 and Fig. 4c). As shown in the right-most column of Table 3, these activation effects in the medial PFCs were mostly significant after correction for family wise error in a priori ROIs derived from a previous study on event-based prospective memory (Okuda et al., 2007), confirming statistical significance and anatomical relevance of the present medial PFC activations.

To test the statistical significance of the interaction effects for the dots and number task, we performed ANOVAs (phase (expanding, contracting) and response type (target, ongoing) as within-subject factors, 16 subjects as a random effect) on mean effect sizes within the medial prefrontal cluster identified by the interaction contrast (plots are shown in Fig. 4d). ANOVAs for both tasks revealed significant interaction effects across phase and response ($F(1,15) = 6.2$, $P = 0.024$ and $F(1,15) = 7.0$, $P = 0.018$ for dots and number tasks, respectively). We also performed paired t-tests to confirm phase differences in the target- and ongoing-related activations for each task. These tests revealed significant differences across phases for all cases ($t(15) = 1.8$, 2.3, 2.6, 2.5 and one-tailed $P = 0.043$, 0.019, 0.010, 0.014 for dots target, dots ongoing, number target, and number ongoing responses, respectively; indicated by asterisks in Fig. 4d).

We also found an opposite direction of the interaction effect (i.e., greater target-related activation in the contracting phase than

Table 3
Effects of phase on target- and ongoing-related brain activations.

Anatomical region (Brodmann area)	Peak MNI coordinates			Z-Score	Cluster size (voxels)	SVC P-Value[a]
	x	y	z			
Effects on activations at target response						
Expand > contract						
Lt. anterior cingulate gyrus (32)/medial frontal gyrus (10)	−18	39	−3	3.95	41	0.013
Rt. anterior cingulate gyrus (32)/medial frontal gyrus (10)	18	39	−6	3.80	64	0.019
Lt. superior frontal gyrus (6)/precentral gyrus (6)	−27	−6	72	3.87	15	
Contract > expand						
Rt. anterior cingulate gyrus (32)	15	9	39	3.83	20	0.017
Rt. hippocampus	24	−3	−24	3.48	6	
Effects on activations at ongoing response						
Expand > contract						
Rt. anterior cingulate gyrus (32)	12	15	36	3.64	7	0.031
Lt. inferior frontal gyrus (9)	−48	9	24	3.97	34	
Lt. middle frontal gyrus (6)	−24	9	60	3.97	21	
Lt. anterior insula (13)	−30	21	6	3.31	9	
Lt. precuneus (7)	−21	−72	39	3.99	15	
Lt. fusiform gyrus (37)	−42	−54	−15	4.06	146	
Rt. fusiform gyrus (37)	51	−48	−15	3.71	23	
Midbrain	−3	−24	−6	3.56	18	
Contract > expand						
Lt. anterior cingulate gyrus (32)/medial frontal gyrus (10)	−9	33	−15	4.21	227*	0.005
Rt. anterior cingulate gyrus (24/32)	6	24	−3	4.83	227*	0.023
Rt. medial frontal gyrus (10)	18	57	0	3.39	7	0.063
Rt. middle frontal gyrus (11)	27	36	−3	3.99	43	0.039
Interaction effects across phase and response						
Expand > contract at target and contract > expand at ongoing						
Rt. anterior cingulate gyrus (24/32)	3	27	0	4.97	320#	0.014
Rt. medial frontal gyrus (10)	18	42	−6	4.40	320#	0.002
Lt. anterior cingulate gyrus (24/32)	−9	24	0	4.68	320#	0.049
Lt. medial frontal gyrus (10)	−15	36	−3	4.41	320#	0.003
Contract > expand at target and Expand > contract at ongoing						
Rt. anterior cingulate gyrus (32)	12	15	36	4.58	40	0.001
Lt. fusiform gyrus (37)/	−42	−51	−15	3.98	32	
Middle occipital gyrus (37)	−42	−66	−3	3.57	34	

SVC: small volume correction.

[a] Regions of interests for corrected P values were drawn as 16 mm (twice as large as the spatial smoothing size applied to the fMRI data) radius spheres centered at ($x = −9$, $y = 51$, $z = −9$) for the left medial prefrontal region and ($x = 12$, $y = 45$, $z = −3$) for the right medial prefrontal region, based on (de)activation peak revealed by event-based prospective memory task in a previous report (Okuda et al., 2007, Study 1, ongoing minus event contrast in Table 1). A region of interest for the anterior cingulate cortex was drawn as a 16 mm radius sphere centered at ($x = 12$, $y = 18$, $z = 48$) from data reported in Morishima et al. (2010) (a region that showed involvement in reactive control in a Stroop interference task). Lt.: left. Rt.: right. * and # indicate multiple sub-peaks in a same cluster.
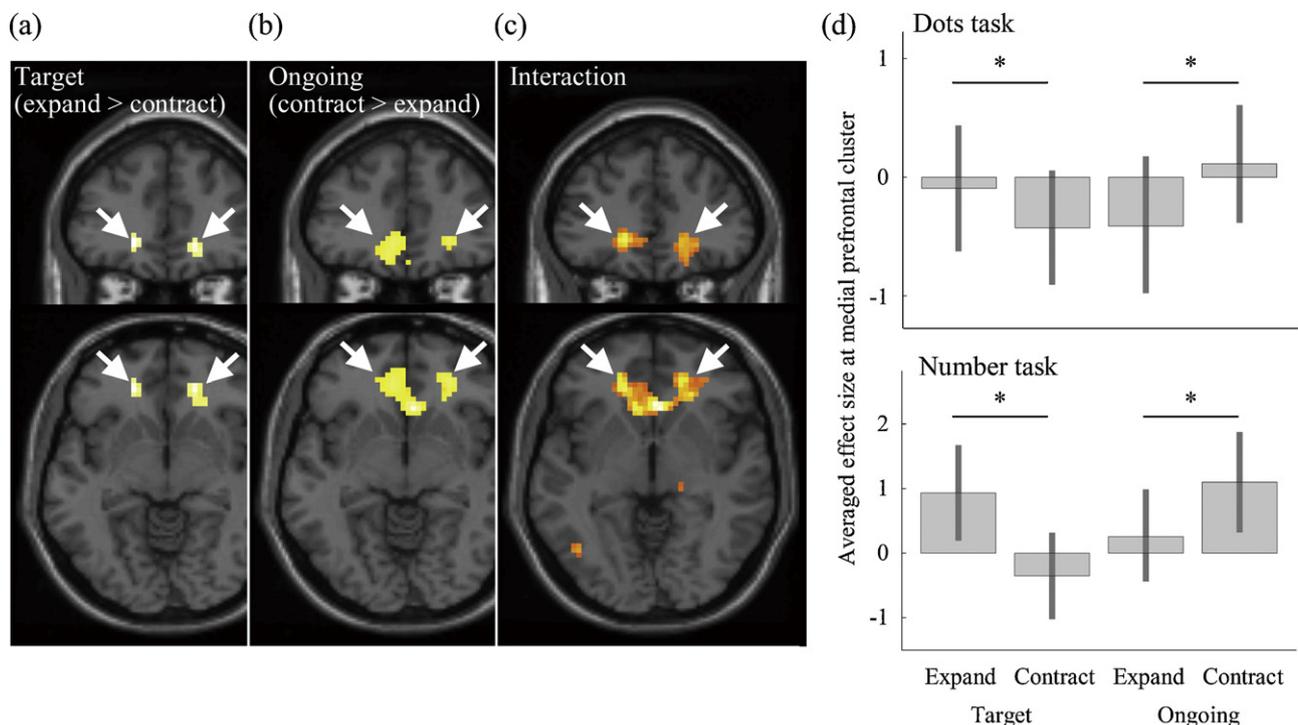
Fig. 4. Medial prefrontal activations showing an interaction effect across response (target/ongoing) and phase (expand/contract). (a) Bilateral medial prefrontal cortices showed significant activations at target response during expanding phase as compared with those during contracting phase. (b) Similar areas of the bilateral medial prefrontal cortices showed significant activations at ongoing responses during contracting phase as compared with those during expanding phase. (c) The medial prefrontal region showed a significant interaction effect across response and phase (a contrast of expanding phase minus contracting phase for target response plus contracting phase minus expanding phase for ongoing response). (d) Averaged effect size at medial prefrontal cluster defined by the interaction results showed significant difference across phases for both target-related and ongoing-related activations in both dots and number tasks. The effect size was plotted relative to that during the baseline task of visually guided simple button press. Error bars show 90% confidence interval. $^{*}P < 0.05$ by a paired t-test.

in the expanding phase, and greater ongoing-related activation in the expanding phase than in the contracting phase, Table 3) in the right anterior cingulate cortex (ACC, Fig. 5). These activation effects in the ACC were also significant after correction for family wise error in the ROI drawn from the previous study regarding the regulation of behavioural interference (Morishima et al., 2010). In a similar manner to the medial prefrontal cluster, ANOVAs (phase (expanding, contracting) and response type (target, ongoing) as within-subject factors, 16 subjects as a random effect) on mean effect sizes within the anterior cingulate cluster revealed significant interaction effects across phase and response ($F(1,15) = 6.5$, $P = 0.022$ and $F(1,15) = 16.2$, $P = 0.001$ for dots and number tasks, respectively). Moreover, the anterior cingulate region also showed significant main effects of response type ($F(1,15) = 26.3$, $P < 0.001$ and $F(1,15) = 21.0$, $P < 0.001$ for dots and number tasks, respectively). Paired t-tests confirmed significant differences in target- and ongoing-related activations across phases ($t(15) = 1.8$, 2.5, 3.5, 2.2 and one-tailed $P = 0.047$, 0.013, 0.002, 0.024 for dots target, dots ongoing, number target, and number ongoing responses, respectively; indicated by asterisks in Fig. 5d).

In addition to these main analyses, we also examined specific effects of hit and secondary correction prospective memory responses on target- and ongoing-related brain activations. For this analysis, we constructed another general linear model for each subject that separately modeled hit and secondary correction responses to targets and corresponding ongoing trials just before the hit and secondary target responses. We again subtracted the baseline condition from these event-related conditions, and then entered the corresponding contrast images into a second level random effect analysis across 16 subjects (ANOVA model with 16 conditions comprising 2 tasks (dots, numbers), 2 response types (target, ongoing), 2 phases (expanding, contracting), and 2 trial

categories (hit and secondary correction), without constant term). Since the behavioural data suggested that the expanding and contracting phases, respectively, tended to elicit hit and secondary correction responses to targets, we specifically examined whether the interaction effects in brain activation differed between this set of conditions (hit trials in expanding phase and secondary correction trials in contracting phase) and the other set of conditions (secondary correction in expanding phase and hit in contracting phase). Thus we performed ANOVAs (phase (expanding, contracting) and response type (target, ongoing) as within-subject factors, 16 subjects as a random effect) on mean effect sizes in the medial prefrontal cluster and the anterior cingulate cluster, separately for the first and second set of conditions (activation plots are shown in Fig. 6). These analyses revealed significant interaction effects in the first set of conditions for both regions (medial prefrontal cluster: $F(1,15) = 8.2$, $P = 0.013$ and $F(1,15) = 9.8$, $P = 0.008$ for dots and number tasks, respectively, anterior cingulate cluster: $F(1,15) = 7.9$, $P = 0.014$ and $F(1,15) = 5.8$, $P = 0.032$ for dots and number tasks, respectively), whereas those in the second set of conditions were not significant (medial prefrontal cluster: $F(1,15) = 1.9$, $P = 0.19$ and $F(1,15) = 3.4$, $P = 0.086$ for dots and number tasks, respectively, anterior cingulate cluster: $F(1,15) = 1.1$, $P = 0.31$ and $F(1,15) = 0.06$, $P = 0.82$ for dots and number tasks, respectively). Therefore, analyses regarding hit and secondary correction responses to prospective memory targets suggested that the opposite phase effects across target- and ongoing-related activations were related primarily to hit trials in the expanding phase and secondary correction trials in the contracting phase.

Finally, we examined patterns of the medial PFC and ACC activations within each expanding and contracting phase to test if there were consistent increase or decrease of activations according to increase/decrease of target intervals in each phase. We constructed
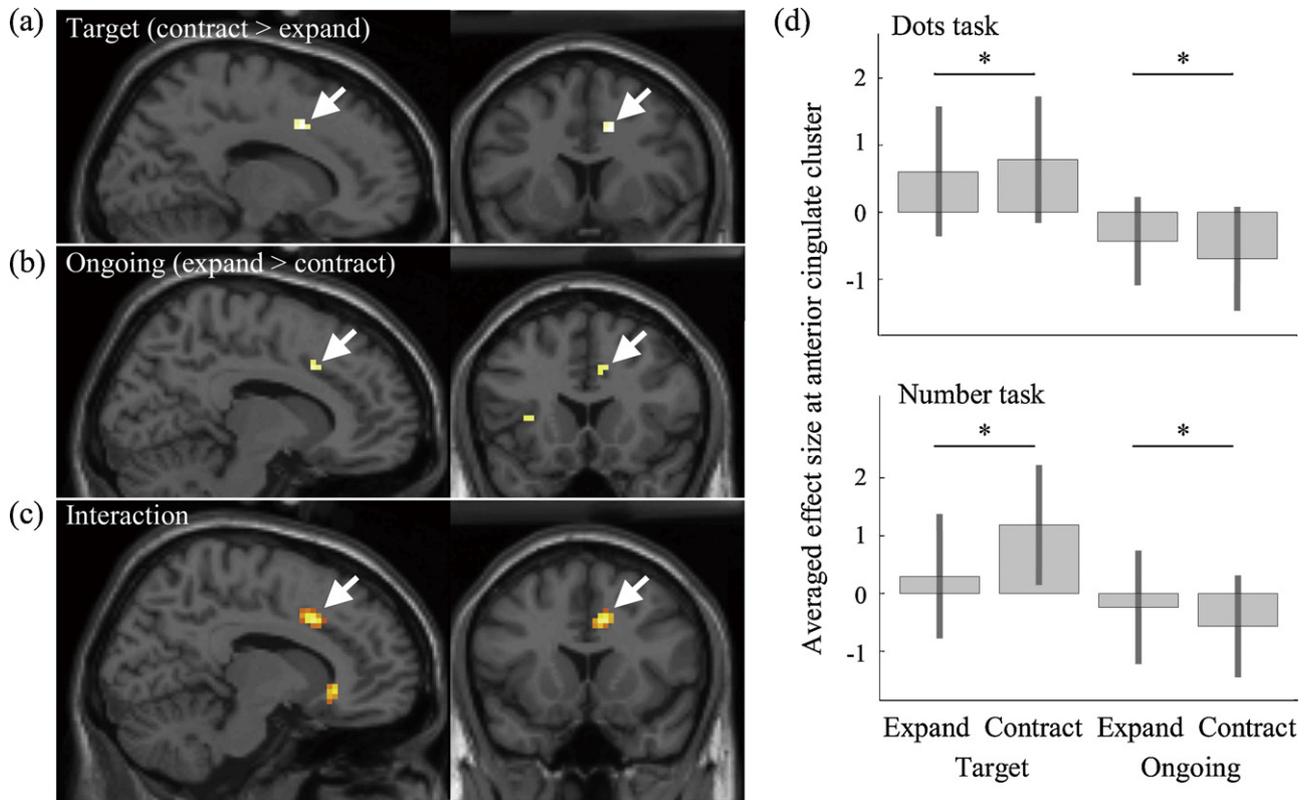
Fig. 5. Anterior cingulate activation showing an interaction effect across response (target/ongoing) and phase (expand/contract). (a) Right anterior cingulate cortex showed significant activation at target response during contracting phase as compared with that during expanding phase. (b) Similar area of the right anterior cingulate cortex showed significant activation at ongoing responses during expanding phase as compared with that during contracting phase. (c) The anterior cingulate region showed a significant interaction effect across response and phase (a contrast of contracting phase minus expanding phase for target response plus expanding phase minus contracting phase for ongoing response), which was opposite direction to the effect in the medial prefrontal region. (d) Averaged effect size at the anterior cingulate cluster defined by the interaction results showed significant difference across phases for both target-related and ongoing-related activations in both dots and number tasks. The effect size was plotted relative to that during the baseline task of visually guided simple button press. Error bars show 90% confidence interval. *$P < 0.05$ by a paired t-test.

further general linear models that separated target and ongoing regressors at each target distance (i.e., expanding target/ongoing trials with target intervals of 8 trials, 12 trials, 16 trials, and 20 trials, and contracting target/ongoing trials with target intervals of 16 trials, 12 trials, 8 trials, and 4 trials), and entered subject-specific contrast images into a random effect model across subjects (ANOVA model with 32 conditions comprising 2 tasks (dots, numbers), 2 response types (target, ongoing), 2 phases (expanding, contracting), and 4 target intervals (8, 12, 16, 20 for the expanding phase and 4, 8, 12, 16 for the contracting phase), without constant term). We specifically examined if there were differential effects of target intervals across phases for each task and response type. For this purpose, we examined interaction effects across phase and target intervals with ANOVAs (phase (expanding, contracting) and target interval (8, 12, 16, 20 for the expanding phase and 4, 8, 12, 16 for the contracting phase) as within-subject factors, 16 subjects as a random effect) on the mean effect sizes in the medial prefrontal cluster and the anterior cingulate cluster for the dots target, dots ongoing, number target, and number ongoing responses (activation plots are depicted in Fig. 7). For the medial PFC cluster, significant interaction across phase and target interval was found only in the dots target response ($F(2,30) = 4.43$, $P = 0.023$). For the ACC cluster, significant interaction effects were found in the dots ongoing ($F(2,30) = 10.1$, $P < 0.001$) and number ongoing ($F(2,30) = 6.30$, $P = 0.005$) responses. Visual inspection of the activation plots (Fig. 7) suggested a clear cross-over pattern (monotonic increase in contracting phase and decrease in expanding phase) in the ACC ongoing responses, but such a consistent pattern was less evident in the other cases.

4. Discussion

4.1. Effects of target intervals on prospective remembering

To our knowledge, the present study is the first to demonstrate empirical data showing how variation of target intervals modulates behavioural and neural responses during prospective memory tasks. In the present experiment, we manipulated intervals of prospective memory target trials so that they were expanding and contracting systematically. By this procedure, we aimed to examine changes in subjects' attentional orientation towards prospective memory targets and ongoing tasks during performance of a single task, without being contaminated by insertion of any qualitatively different task demands. As a result, we found a clear behavioural and neurobiological trade-off between responses to ongoing and prospective memory target trials across expanding and contracting target intervals. Since we did not add any specific task components that differed between the two (hidden) phases as outlined above, the observed trade-off effect cannot be regarded a consequence of any difference in explicit task requirements, but probably reflects an adaptive mechanism engaged in response to the embedded target schedule. As such, the present study shows that manipulation of the trial sequence can reveal behavioural measures of subjects' attentional allocation without introducing any confounds arising from changes in tasks.

Another important aspect of the present experimental design was the ability to examine the effects of *changes* in target intervals over time (which can be regarded a "second-order" variation, or a "history effect", in target intervals), rather than those related to
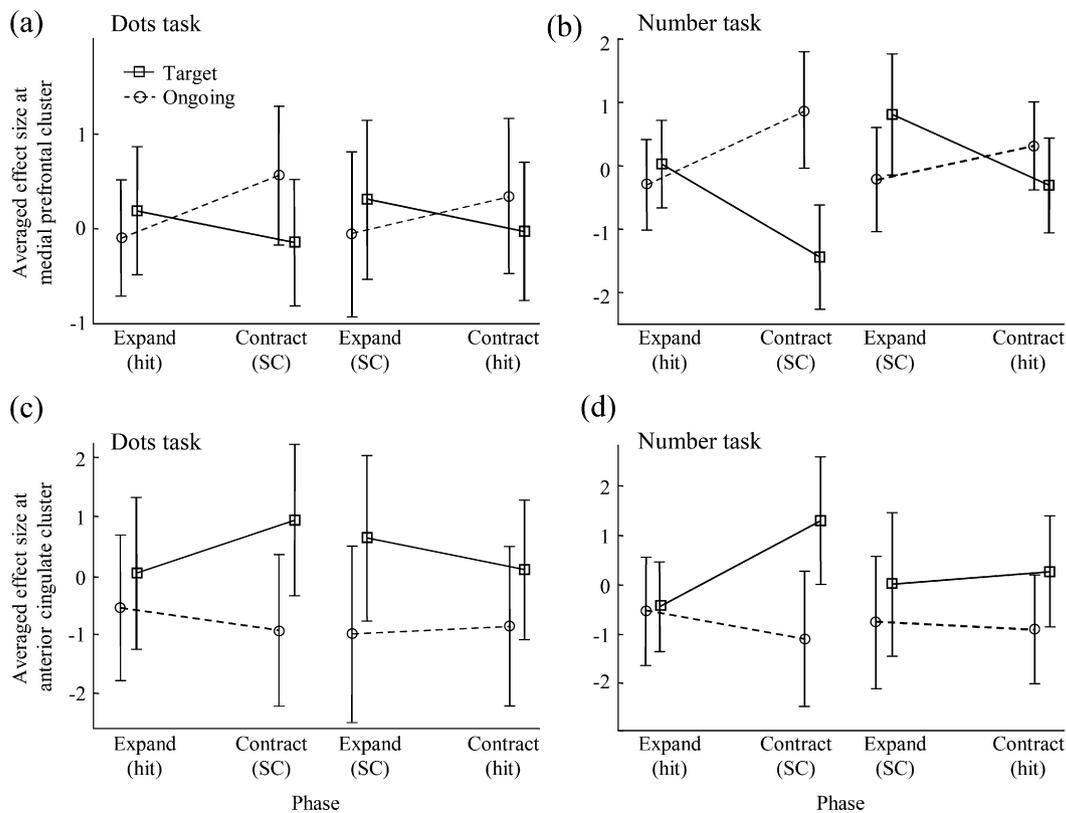
Fig. 6. Activation profiles of medial prefrontal and anterior cingulate clusters across trials with target hit and secondary correction responses. Averaged effect size at (a and b) medial prefrontal cluster and (c and d) anterior cingulate cluster was plotted separately for two sets of conditions according to hit/secondary correction (SC) prospective memory responses (first set: hit trials in expanding phase and SC trials in contracting phase, second set: SC in expanding phase and hit in contracting phase). The first set was consistent with the behavioural effects but the second set was not. Error bars show 90% confidence interval. The data showed significant interaction effects across response (target/ongoing) and phase (expand/contract) for the first set but not for the second set in all cases.

each length of target interval itself (considered as a "first-order" variation or a local frequency of the target occurrence). That is, the target interval itself was completely matched across the expanding and contracting phases (the same 8, 12, and 16 intervals) in the present design: only temporal orders of the target interval differed across the phases. By this manipulation, we successfully identified that the subjects' behaviour and brain activities were sensitive to "relative" target intervals compared to the past interval. A target occurrence later than the previous target interval (expanding phase) promoted more successful and faster responses to the target, with a cost of lower and slower performance of the ongoing tasks; vice versa for target occurrence earlier than the previous interval (contracting phase). These effects cannot simply be explained by a single factor indexing temporal decay of memory traces for the target events, or a continuous build-up of expectation to the next prospective memory target, since each target-to-target distance was equated across phases as mentioned above. Rather, the results suggest that the possible memory representation or expectation to prospective memory targets may better be considered in relation to latest experiences of target events.

One possible mechanism for the brain to establish such a temporal effect in the current experimental paradigm would be accumulation of past dynamics of target occurrence during the phases. In other words, information about whether the current phase was expanding or contracting would be only available as the target interval went up or down. If such a temporal accumulation was the major strategy, then we may expect linear changes of brain activations as well as behavioural performance within each phase, possibly with opposite direction of changes across expanding and contracting phases. However, we did not find consistent

evidence for linear increase/decrease in brain activations (Fig. 7) and behavioural measures (Tables 1 and 2) in the present results, although a few cases showed significant trends. The lack of consistent evidence for within-phase changes might be partly because of insufficient statistical power to find the effect, or potential nonlinear effects described in Section 2. Our present design had only 3–4 data points during each phase with relatively short event intervals in order to maximize statistical efficiency to detect overall differences across phases (numbers of repetitions of phases, rather than within-phase data points and duration between two successive target events, were maximized). Alternatively, the lack of within-phase effect might also be explained by the constant rate of changes in two successive target intervals: the difference between current and previous target intervals was constant in the present experiment (always 4 trials later than previous in the expanding phase and always 4 trials earlier than previous in the contracting phase). That is, a possible mechanism underlying current results might be "moment-to-moment comparison" rather than "temporal accumulation" of target experiences: neural processes identified here may be those sensitive to a local comparison between current and immediately previous target intervals that may help efficient adaptation to the changing environment, rather than accumulation processes for a longer history of past data.

Previously, a few studies have examined the effects of target intervals (or frequency) on target-related cognitive processes. For example, Herron, Henson, and Rugg (2004) reported that the probability of target events over non-target events could have a specific effect on recognition judgments on the target. Another study (Huettel, Mack, & McCarthy, 2002) examined the effects of length of temporal patterns embedded in a continuous trial
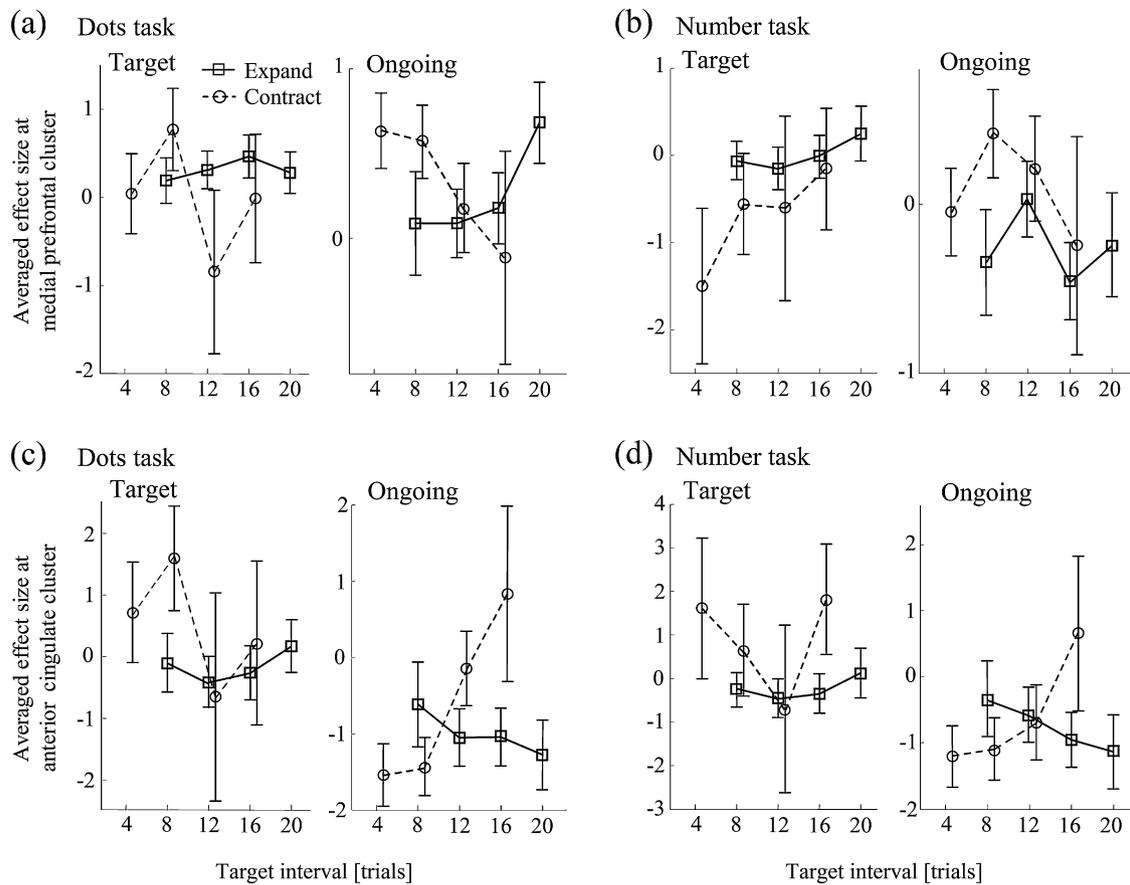
Fig. 7. Activation profiles of medial prefrontal and anterior cingulate clusters at each target interval across expanding and contracting phases. Averaged effect size in the dots and number tasks at (a and b) medial prefrontal cluster and (c and d) anterior cingulate cluster was plotted separately for target-related and ongoing-related activations. Error bars show 90% confidence interval.

sequence (continuation; A-A-A-A-··· or alteration; A-B-A-B-···) on latency and brain activation for processing of trial events that violated the continuous sequence pattern. These studies showed a linear dependency of activation in lateral areas of the PFC on the frequency of target occurrence (Herron et al., 2004) or the length of continuous sequence patterns (Huettel et al., 2002), both of which can be regarded as a measure of first-order temporal variation of task trial intervals. In contrast, our data revealed activation changes only in the medial PFCs in relation to the relative changes in target intervals (second-order variation). Therefore, our data together with the previous findings may suggest that distinct cognitive systems are involved in processing of direct (first-order variation) and relative (second-order variation) representations of target intervals, with differential roles played by the lateral and medial PFCs. We speculate that there may be a process specifically involving the medial PFCs that provides moment-to-moment predictive simulation of events occurring in external world by receiving information about temporal patterns of recent experiences that are possibly expressed in the lateral PFCs. Recent studies showing medial PFC involvement in predictive judgment on uncertain perception (Bar, 2004; Summerfield et al., 2006) as well as episodic simulation of future events (Okuda et al., 2003; Schacter, Addis, & Buckner, 2008) are consistent with this view.

4.2. Automatic nature of attentional coordination

It is noteworthy that the trade-off effects in the present results, which were consistently observed in response accuracy and reaction time measures, as well as in activation patterns in the medial frontal areas, occurred despite participants reporting no awareness

of the periodic change in target intervals, or use of this information to strategically prepare for the next target. As such, we argue that the observed effects are primarily attributable to the automatic capturing of attention by the experience of target events. In other words, the present results implicate that attentional regulation between ongoing processing and prospective memory response does not necessarily accompany a conscious, strategic search process intentionally controlled by subjects. Our experimental design, just manipulating the temporal sequence of target events, reveals that this kind of behavioural regulation can be achieved simply in response to changes in the temporal pattern of target occurrence, without any explicit task instructions or subjects' conscious effort. Therefore, our data suggest that reactive mechanisms for coordinating attentional resources may play more predominant roles in prospective remembering than has been assumed previously.

The implicit nature of the behavioural effects might be related to a degree to which memory representation of the prospective target response has been stored into long-term memory beyond working memory capacity. It is thought that long-term memory does not necessarily accompany conscious and continuous attention to memory representations, while the working memory is believed to require on-line, active maintenance of memory representations. Although the present study was not designed to investigate the degree of working/long-term memory involvement explicitly, indirect evidence from the present results may support involvement of the long-term memory system in the present behavioural effects: there was a tendency that the behavioural effects were observed more frequently at longer (12 and 16) target distances (numbers of occasions manifesting significant differences across phases in behavioural performance/RT were 6, 12, and 11 at target distance of

8, 12, and 16, respectively, see asterisks in Tables 1 and 2). It might be speculated that the longer target distances promoted greater involvement of the long-term memory system than the working memory system. In other words, the data might suggest existence of potential nonlinear effects according to the target distance also in the behavioural/psychological level. Related to the discussion about the possible within-phase changes and nonlinearity across different target time courses, exact relation between the target distance (the first-order temporal factor), long-term/working memory involvement, and automatic/controlled retrieval in prospective memory should be an important research question in future works.

4.3. Roles of the anterior part (area 10) of the medial PFC in attentional regulation

In searching for brain regions involved in this kind of automatic coordination of attention, we found that areas in the medial PFC showed consistent trade-off effects in target-related and ongoing-related activations across the expanding and contracting target intervals. These included the anterior part of the medial PFC encompassing BA 10, as well as a more posterior part in the ACC. Previously, activation changes in medial BA 10 have been consistently identified in neuroimaging studies of prospective memory. A typical activity pattern in this region is an activation decrease during event-based prospective memory tasks, requiring detection of target events during ongoing activities, as compared with baseline tasks in which subjects are engaged in the ongoing activity alone (Burgess et al., 2003; Gilbert et al., 2009; Simons et al., 2006). One exception to this deactivation pattern has been observed in time-based prospective memory tasks (Okuda et al., 2007). In such tasks, rather than being cued by unpredictable ongoing task events, realization of the delayed intention is required at a particular time, determined either by a separate visually presented clock or by the participant's own estimation of the passage of time.

Based on these observations (as well as other related neuroimaging results and neuropsychological investigations), Burgess, Gilbert, Dumontheil, and Simons (2005), Burgess, Gilbert, Okuda, and Simons (2006), and Burgess, Dumontheil, and Gilbert (2007), have proposed the gateway hypothesis of rostral PFC (BA 10) function. According to this hypothesis, medial and lateral BA 10, respectively, are involved in orientation of attention towards externally presented stimuli (including both ongoing and prospective memory target stimuli) and internally maintained thoughts such as delayed intentions. The medial BA 10 activation patterns observed in the present study can be understood in relation to this hypothesis. Specifically, the medial BA 10 activation observed in association with the more successful and faster prospective memory target responses in the expanding target interval phase can be regarded as reflecting higher levels of anticipatory attention towards appearance of the prospective memory targets. Similarly, activation in the same medial region in association with the faster ongoing responses in the contracting target interval phase may reflect a higher level of concentration on currently relevant task stimuli, as compared with higher tendency of disengagement from the ongoing task stimuli in the expanding target interval phase. Consistent with this interpretation, trade-off effects in the medial BA 10 activation were more prominent for periods involving secondary correction prospective memory responses in the contracting phase and prospective memory hit responses in the expanding phase (Fig. 6). Importantly, these effects cannot simply be considered to reflect reaction times *per se* as we covaried out the trial-by-trial variance in reaction times in the design matrix of the fMRI analysis (see also Gilbert, Spengler, Simons, Frith, & Burgess, 2006 for detailed discussion about correlation between RT and brain activation). Taken together, the results suggest that the activity level of medial BA 10 is relevant to subjects' attentional orientation, rather

than merely reflecting temporal pattern of the stimulus input or subjects' motor output.

Additionally, the present results may add to the gateway hypothesis by suggesting that the processing balance between external stimuli and internal thoughts could be regulated in an automatic fashion. As we discussed above, the behavioural modulation accompanying activation changes in the anterior medial PFC in the present results would reflect automatic, rather than controlled, regulation of attention in response to the experience of target events. Whether the attentional biasing is realized in an automatic fashion or by means of a controlled process has been unclear in the existing studies investigating the gateway hypothesis. The present data suggest that at the least the stimulus-oriented attention mediated by the medial PFC may primarily be coordinated reflexively by (sequences of) environmental input.

We did not find any activation changes in the lateral PFCs during the periodic target interval sequences in the present results. Failure to observe the lateral PFC activation may suggest a possibility that the lateral PFC is more related to conscious, strategic control processes that were less emphasized in the present experiment as discussed above. In relation to this notion, Simons et al. (2006) found greater activation in the lateral BA 10 during a condition in which maintenance and retrieval of prospective memory intention were more demanding, as compared with a condition in which identification of prospective memory target events was more emphasized (with less demands for the intention retrieval component). The present results would also be consistent with Gilbert et al.'s (2009) finding that medial PFC was associated with stimulus-driven responses to prospective memory targets, whereas lateral PFC was more associated with deliberate monitoring for targets. In this way, our findings indirectly suggest two different characteristics of stimulus-oriented and stimulus-independent attending supported by the medial and lateral anterior PFCs: the former may be based principally on automatic, reactive processing, while the latter requires more controlled processes. In support of this view, Gilbert, Frith, and Burgess (2005) showed sustained activation in the medial anterior PFC during stimulus-oriented task processing but transient activation in the lateral anterior PFC at the time of switching between stimulus-oriented and stimulus-independent task processing. It would be reasonable to assume that the attentional orientation towards the external stimuli is largely reactive in response to perturbation by environmental input, whereas attention control towards internal representations against incoming stimuli would be more volitional in nature.

4.4. ACC functions and reactive control

The present results also showed consistent trade-off effects in the activation pattern in the right ACC, which was in the opposite direction to that identified in the anterior medial PFC. The opposite effects across the anterior and posterior parts of the medial frontal cortices suggest complementary functional organization in attentional coordination along the anterior–posterior direction in the midline frontal cortex. Consistent with this hypothesis, in a meta-analysis by Gilbert, Gonen-Yaacovi, Benoit, Volle, and Burgess (2010), ACC tended to co-activate with lateral anterior PFC rather than medial anterior PFC. The pattern of the trade-off in the ACC region was characterized as greater activation at less prepared, surprising target presentation with longer reaction times, as well as greater activation at more interfered ongoing trials with higher levels of anticipation for forthcoming targets. This pattern of the effect is consistent with the well-known hypothesis of conflict-related functions of the ACC (Carter et al., 1998; Kerns et al., 2004; MacDonald, Cohen, Stenger, & Carter, 2000). Previously, the function of the ACC in the detection and resolution of the conflicts has been assumed to reflect strategic control of cognitive

resources to adjust behaviour on demand (Isoda & Hikosaka, 2007; Johnston, Levin, Koval, & Everling, 2007; van Veen & Carter, 2002). A recent fMRI study (Morishima et al., 2010), however, has raised the possibility of more automatic control realized by a network involving the ACC. They estimated trial-by-trial variation in neural activity reflecting the balance between task-relevant and task-irrelevant sensory areas (sensory conflict) in a face–word Stroop task (male/female judgment of stimuli composed of a word "male" or "female" on a male or female face) using deconvolution of fMRI signals. Based on the results that neural activity estimates in an ACC region were significantly correlated with those in a dorsolateral PFC region that reflected amount of the sensory conflict only when high sensory conflict was resolved behaviourally (fast and accurate responses), the authors proposed a reactive control mechanism mediated by a bottom-up neural processing from the posterior sensory areas to the dorsolateral PFC and the ACC. It may be possible that this kind of reactive mechanism underlies the trade-off effect in the present ACC results, which could support reflexive adjustment of attention in the presence of conflicts between ongoing and prospective memory responses.

5. Conclusion

To summarise, the results of the present study have shown a clear example in which attention between current task performance and future action plans in prospective memory is automatically regulated without conscious, strategic control processes. The present fMRI data suggest that medial areas of the frontal cortex mediate such automatic coordination of attentional resources. In light of the gateway hypothesis, we suggest the possibility that the attentional orientation towards external task processing will be coordinated reflexively by the medial PFC according to temporal experiences of environmental input, whereas disengaging from stimulus-oriented processing and then orienting attention towards internally maintained representations such as future plans would require more controlled processes that are probably mediated by lateral PFC.

Acknowledgments

References

Bar, M. (2004). Visual objects in context. *Nature Reviews Neuroscience*, 5(8), 617–629.

Buckner, R. L. (1998). Event-related fMRI and the hemodynamic response. *Human Brain Mapping*, 6(5–6), 373–377.

Buckner, R. L., Goodman, J., Burock, M., Rotte, M., Koutstaal, W., Schacter, D., et al. (1998). Functional-anatomic correlates of object priming in humans revealed by rapid presentation event-related fMRI. *Neuron*, 20(2), 285–296.

Brandimonte, M., Einstein, G. O., & McDaniel, M. A. (1996). *Prospective memory: Theory and applications*. Mahaw, NJ: Lawrence Erlbaum Associates.

Burgess, P. W., Dumontheil, I., & Gilbert, S. J. (2007). The gateway hypothesis of rostral prefrontal cortex (area 10) function. *Trends in Cognitive Sciences*, 11(7), 290–298.

Burgess, P. W., Gilbert, S. J., Dumontheil, I., & Simons, J. S. (2005). The gateway hypothesis of rostral prefrontal cortex (area 10) function. In J. Duncan, L. Phillips, & P. MacLeod (Eds.), *Speed, control, and age: In honour of Patrick Rabbitt* (pp. 217–248). Oxford: Oxford University Press.

Burgess, P. W., Gilbert, S. J., Okuda, J., & Simons, J. S. (2006). Rostral prefrontal brain regions (area 10): A gateway between inner thought and the external world? In

W. Prinz, & N. Sebanz (Eds.), *Disorders of volition* (pp. 373–395). Cambridge, MA: MIT Press.

Burgess, P. W., Quayle, A., & Frith, C. D. (2001). Brain regions involved in prospective memory as determined by positron emission tomography. *Neuropsychologia*, 39(6), 545–555.

Burgess, P. W., Scott, S. K., & Frith, C. D. (2003). The role of the rostral frontal cortex (area 10) in prospective memory: A lateral versus medial dissociation. *Neuropsychologia*, 41(8), 906–918.

Burock, M. A., Buckner, R. L., Woldorff, M. G., Rosen, B. R., & Dale, A. M. (1998). Randomized event-related experimental designs allow for extremely rapid presentation rates using functional MRI. *Neuroreport*, 9(16), 3735–3739.

Carter, C. S., Braver, T. S., Barch, D. M., Botvinick, M. M., Noll, D., & Cohen, J. D. (1998). Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science*, 280(5364), 747–749.

Cohen, A. L., West, R., & Craik, F. I. M. (2001). Modulation of the prospective and retrospective components of memory for intentions in younger and older adults. *Aging Neuropsychology and Cognition*, 8(1), 1–13.

Dale, A. M. (1999). Optimal experimental design for event-related fMRI. *Human Brain Mapping*, 8(2–3), 109–114.

Dale, A. M., & Buckner, R. L. (1997). Selective averaging of rapidly presented individual trials using fMRI. *Human Brain Mapping*, 5(5), 329–340.

Dalla Barba, G. (1989). Prospective memory: A 'new' memory system? In F. Boller, & J. Grafman (Eds.), *Handbook of neuropsychology* (pp. 239–251). Amsterdam: Elsevier Science.

Friston, K. J., Glaser, D. E., Henson, R. N. A., Kiebel, S., Phillips, C., & Ashburner, J. (2002). Classical and Bayesian inference in neuroimaging: Applications. *NeuroImage*, 16(2), 484–512.

Friston, K. J., Price, C. J., Fletcher, P., Moore, C., Frackowiak, R. S., & Dolan, R. J. (1996). The trouble with cognitive subtraction. *NeuroImage*, 4(2), 97–104.

Gilbert, S. J., Frith, C. D., & Burgess, P. W. (2005). Involvement of rostral prefrontal cortex in selection between stimulus-oriented and stimulus-independent thought. *European Journal of Neuroscience*, 21(5), 1423–1431.

Gilbert, S. J., Gollwitzer, P., Cohen, A.-L., Oetinngen, G., & Burgess, P. W. (2009). Separable brain systems supporting cued versus self-initiated realization of delayed intentions. *Journal of Experimental Psychology: Learning, Memory and Cognition*, 35(4), 905–915.

Gilbert, S. J., Gonen-Yaacovi, G., Benoit, R. G., Volle, E., & Burgess, P. W. (2010). Distinct functional connectivity associated with lateral versus medial rostral prefrontal cortex: A meta-analysis. *NeuroImage*, 53(4), 1359–1367.

Gilbert, S. J., Spengler, S., Simons, J. S., Frith, C. D., & Burgess, P. W. (2006). Differential functions of lateral and medial rostral prefrontal cortex (area 10) revealed by brain–behavior associations. *Cerebral Cortex*, 16(12), 1783–1789.

Henson, R. (2004). Analysis of fMRI time series: Linear time-invariant models, event-related fMRI, and optimal experimental design. In R. S. J. Frackowiak, K. J. Friston, C. D. Frith, R. J. Dolan, C. J. Price, S. Zeki, J. Ashburner, & W. Penny (Eds.), *Human brain function* (2nd ed., pp. 793–822). San Diego: Academic Press.

Herron, J. E., Henson, R. N. A., & Rugg, M. D. (2004). Probability effects on the neural correlates of retrieval success: An fMRI study. *NeuroImage*, 21(1), 302–310.

Huettel, S. A., Mack, P. B., & McCarthy, G. (2002). Perceiving patterns in random series: Dynamic processing of sequence in prefrontal cortex. *Nature Neuroscience*, 5(5), 485–490.

Isoda, M., & Hikosaka, O. (2007). Switching from automatic to controlled action by monkey medial frontal cortex. *Nature Neuroscience*, 10(2), 240–248.

Johnston, K., Levin, H. M., Koval, M. J., & Everling, S. (2007). Top-down control-signal dynamics in anterior cingulate and prefrontal cortex neurons following task switching. *Neuron*, 53(3), 453–462.

Jung, K. (2009). A nonlinear BOLD model accounting for refractory effect by applying the longitudinal relaxation in NMR to the linear BOLD model. *Magnetic Resonance Imaging*, 27(7), 907–912.

Kerns, J. G., Cohen, J. D., MacDonald, A. W., III, Cho, R. Y., Stenger, V. A., & Carter, C. S. (2004). Anterior cingulate conflict monitoring and adjustments in control. *Science*, 303(5660), 1023–1026.

MacDonald, A. W., III, Cohen, J. D., Stenger, V. A., & Carter, C. S. (2000). Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science*, 288(5472), 1835–1838.

Marsh, R. L., & Hicks, J. L. (1998). Event-based prospective memory and executive control of working memory. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 24(2), 236–349.

Marsh, R. L., Hicks, J. L., Cook, G. I., Hansen, J. S., & Pallos, A. L. (2003). Interference to ongoing activities covaries with the characteristics of an event-based intention. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 29(5), 861–870.

McDaniel, M. A., & Einstein, G. O. (1993). The importance of cue familiarity and cue distinctiveness in prospective memory. *Memory*, 1(1), 23–41.

McDaniel, M. A., & Einstein, G. O. (2000). Strategic and automatic processes in prospective memory retrieval: A multiprocess framework. *Applied Cognitive Psychology*, 14, S127–S144.

Meacham, J. A., & Singer, J. (1977). Incentive effects in prospective remembering. *Journal of Psychology*, 97, 191–197.

Morishima, Y., Okuda, J., & Sakai, K. (2010). Reactive mechanism of cognitive control system. *Cerebral Cortex*, 20(11), 2675–2683.

Okuda, J., Fujii, T., Ohtake, H., Tsukiura, T., Tanji, K., Suzuki, K., et al. (2003). Thinking of the future and past: The roles of the frontal pole and the medial temporal lobes. *NeuroImage*, 19(4), 1369–1380.

Okuda, J., Fujii, T., Ohtake, H., Tsukiura, T., Yamadori, A., Frith, C. D., et al. (2007). Differential involvement of regions of rostral prefrontal cortex (Brodmann area 10) in time- and event-based prospective memory. *International Journal of Psychophysiology*, *64*(3), 233–246.

Okuda, J., Fujii, T., Yamadori, A., Kawashima, R., Tsukiura, T., Fukatsu, R., et al. (1998). Participation of the prefrontal cortices in prospective memory: Evidence from a PET study in humans. *Neuroscience Letters*, *253*(2), 127–130.

Schacter, D. L., Addis, D. R., & Buckner, R. L. (2008). Episodic simulation of future events: Concepts, data, and applications. *Annals of New York Academy of Sciences*, *1124*, 39–60.

Simons, J. S., Schölvinck, M. L., Gilbert, S. J., Frith, C. D., & Burgess, P. W. (2006). Differential components of prospective memory? Evidence from fMRI. *Neuropsychologia*, *44*(8), 1388–1397.

Smith, R. E. (2003). The cost of remembering to remember in event-based prospective memory: Investigating the capacity demands of delayed intention performance. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *29*(3), 347–361.

Smith, R. E., & Bayen, U. J. (2004). A multinomial model of event-based prospective memory. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *30*(4), 756–777.

Sternberg, S. (1969). Memory-scanning: Mental processes revealed by reaction-time experiments. *American Sciences*, *57*(4), 421–457.

Summerfield, C., Egner, T., Greene, M., Koechlin, E., Mangels, J., & Hirsch, J. (2006). Predictive codes for forthcoming perception in the frontal cortex. *Science*, *314*(5803), 1311–1314.

van Veen, V., & Carter, C. S. (2002). The anterior cingulate as a conflict monitor: fMRI and ERP studies. *Physiology & Behavior*, *77*(4–5), 477–482.

Wager, T. D., Vazquez, A., Hernandez, L., & Noll, D. C. (2005). Accounting for nonlinear BOLD effects in fMRI: Parameter estimates and a model for prediction in rapid event-related studies. *NeuroImage*, *25*(1), 206–218.