Endogenous-cue prospective memory involving incremental updating of working memory: an fMRI study
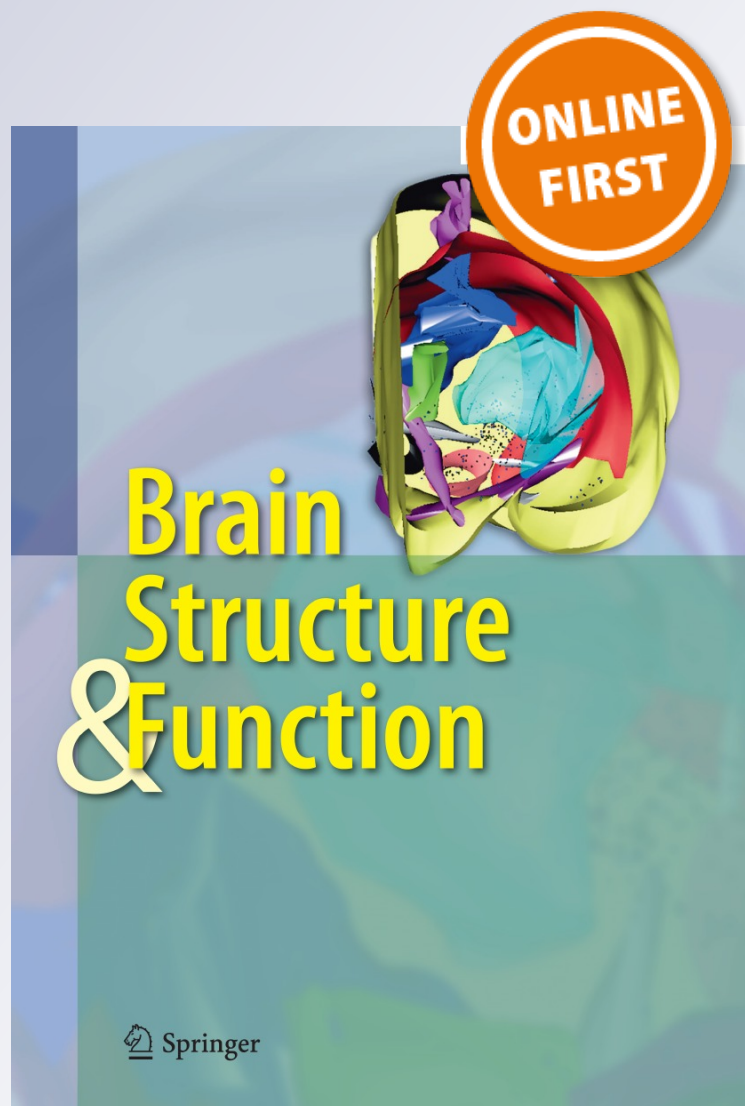
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Endogenous-cue prospective memory involving incremental updating of working memory: an fMRI study

Harsha N. Halahalli · John P. John ·
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Abstract

Introduction Prospective memory paradigms are conventionally classified on the basis of event-, time-, or activity-based intention retrieval. In the vast majority of such paradigms, intention retrieval is provoked by some kind of external event. However, prospective memory retrieval cues that prompt intention retrieval in everyday life are commonly endogenous, i.e., linked to a specific imagined retrieval context. We describe herein a novel prospective memory paradigm wherein the endogenous cue is generated by incremental updating of working memory, and investigated the hemodynamic correlates of this task.
Methods Eighteen healthy adult volunteers underwent functional magnetic resonance imaging while they performed a prospective memory task where the delayed intention was triggered by an endogenous cue generated by incremental updating of working memory. Working memory and ongoing task control conditions were also administered.
Results The 'endogenous-cue prospective memory condition' with incremental working memory updating was associated with maximum activations in the right rostral prefrontal cortex, and additional activations in the brain regions that constitute the bilateral fronto-parietal network, central and dorsal salience networks as well as cerebellum. In the working memory control condition, maximal activations were noted in the left dorsal anterior insula.
Conclusions Activation of the bilateral dorsal anterior insula, a component of the central salience network, was found to be unique to this 'endogenous-cue prospective memory task' in comparison to previously reported exogenous- and endogenous-cue prospective memory tasks without incremental working memory updating. Thus, the findings of the present study highlight the important role played by the dorsal anterior insula in incremental working memory updating that is integral to our endogenous-cue prospective memory task.

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Introduction

Prospective memory (PM) refers to the ability to perform an intended action after a delay and involves intention encoding, intention maintenance over a delay interval while being engaged in another (ongoing) task, monitoring, cue detection, and intention retrieval and execution (Burgess et al. 2003; Kliegel et al. 2000). Prospective memory has been traditionally classified as event-, time-, or activity-based intention retrieval (Kvavilashvili and Ellis 1996; Dismukes 2010). The intention retrieval context in a vast majority of the above tasks is provoked by an external event, i.e., an *exogenous* cue (Kliegel et al. 2008; Dismukes 2010; Brewer et al. 2011). However, prospective memory cues that prompt intention retrieval in everyday life are commonly endogenous, i.e., linked to an imagined retrieval context (e.g., remembering to make a phone call before going to a meeting; remembering to carry out an action after a particular time interval), the cue for which is not explicitly provided (Okuda et al. 2007). Human lesion studies (Daum and Mayes 2000) and an emerging body of neuroimaging studies (Burgess et al. 2011; Volle et al. 2011) have consistently shown participation of the rostral prefrontal cortex (rPFC/BA10)-guided fronto-parietal (FP) network in intention maintenance during both endogenous and exogenous prospective memory tasks. Further, it is suggested that rPFC acts as a "gateway" in switching between stimulus-oriented and stimulus-independent cognition (Burgess et al. 2007).

Prospective memory tasks that involve retrieval of a predefined 'endogenous' cue have been described recently (Benoit et al. 2012). The rPFC was shown to be critically involved in maintaining and/or implementing the delayed intention in the above 'endogenous-cue' prospective memory task. However, 'endogenous-cue prospective memory tasks' that require incremental updating of working memory (WM) for generation of the intention retrieval context have not been described so far. A real-life example of this might be if you want to organize a stack of ten dollar notes into bundles amounting to 100 dollars each, you have to keep counting the notes one by one, and remember to bundle them upon the money count reaching 100 dollars, instead of performing the ongoing task of picking up the next ten dollar note for counting. Here, the generation of the prospective memory intention retrieval context is contingent on the incremental updating of working memory through the act of counting each ten dollar note leading up to a count of 100. Thus, a critical component that differentiates such tasks from previously described 'endogenous-cue prospective memory tasks' is the incremental updating of working memory that dynamically generates the intention retrieval context. This contrasts with the predefined 'endogenous' intention retrieval context described in Benoit et al. (2012) above.

We describe herein an fMRI prospective memory paradigm that requires incremental updating of working memory for generation of the intention retrieval context. Complex working memory tasks have been shown to be related to maximal activity in the 'salience network' (Seeley et al. 2007; Sridharan et al. 2008) comprising the dorsal anterior insula and anterior cingulate cortex (ACC) (Engstrom et al. 2013). Moreover, the salience network has been shown to be crucial for marking those external stimuli as 'salient', which require further access to attentional and working memory processes (Palaniyappan et al. 2013; Menon and Uddin 2010). Given the requirement of working memory updating with each successive trial for generating the intention retrieval context in our paradigm, the stimulus presented with each trial (in this case, an Arabic numeral presented in the central square) is expected to cause pronounced activation of the salience network. This pronounced activation of the salience network during detection of salient events could initiate switches between networks involved in self-related internally oriented processing and those involved in goal-directed externally oriented processing (Uddin et al. 2014) for generation of the endogenous-cue and retrieval of the intention, while incrementally updating the working memory in response to the presented Arabic numerals. We compared the fMRI blood oxygen level dependent (BOLD) signal between the prospective memory task and a control ongoing task (OT) to examine the brain regions that are associated with endogenous prospective memory involving incremental updating of working memory. To confirm whether the dorsal anterior insula and anterior cingulate cortices that constitute the salience network are critical for the performance of the incremental working memory updating component of the prospective memory task, we administered the working memory component as a separate task and compared the BOLD signal during the performance of the task with that during the ongoing task. We hypothesized that in the prospective memory versus ongoing task (PM-OT) contrast in our experiment, there would be activations of the brain regions that constitute the salience network viz., dorsal anterior insula and anterior cingulate, in addition to activations of areas that have already been linked robustly with prospective memory, for e.g., the rPFC and fronto-parietal brain regions. For the working memory versus ongoing task (WM-OT) contrast, we expected maximum activations in the dorsal anterior insula and anterior cingulate, in view of the critical role played by salience network in the working memory component that is integral to our prospective memory task.

Materials and methods

The study was carried out at the National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India,

with due approval from the Institute Ethics Committee thus conforming to the ethical standards laid down in the 1964 Declaration of Helsinki. Written informed consent was obtained from all the participants prior to enrollment into the study.

Study sample

The study sample comprised eighteen healthy volunteers (13 males) recruited by word of mouth from the NIMH-ANS campus community. The subjects were ascertained to be free from Axis I or II psychiatric disorders using the Mini-International Neuropsychiatric Interview (MINI) Plus (Sheehan et al. 1998). Medical/neurological conditions requiring regular medications, current use of psychotropic drugs as well as history of psychotic disorders in first-degree relatives in the subjects were ruled out by an unstructured clinical interview. Only right-handed subjects as determined by modified Annett's inventory (Annett 1976), with a Mini–Mental Status Examination (MMSE) score of ≥23 (Folstein et al. 1975) were recruited into the study. The matrix reasoning module of Wechsler's Adult Intelligence Scale-III (WAIS-III) (Wechsler 1997) was administered to all participants to obtain an estimate of their perceptual organization index as a reflection of their intellectual abilities, independent of verbal abilities. The study sample had a mean age of 26 years (range 18–35 years; SD = 5.15), mean education level of 13.61 years (range 10–18 years; SD = 2.68) and a mean WAIS-III matrix reasoning score of 13.78 (range 7–22; SD = 5.65).
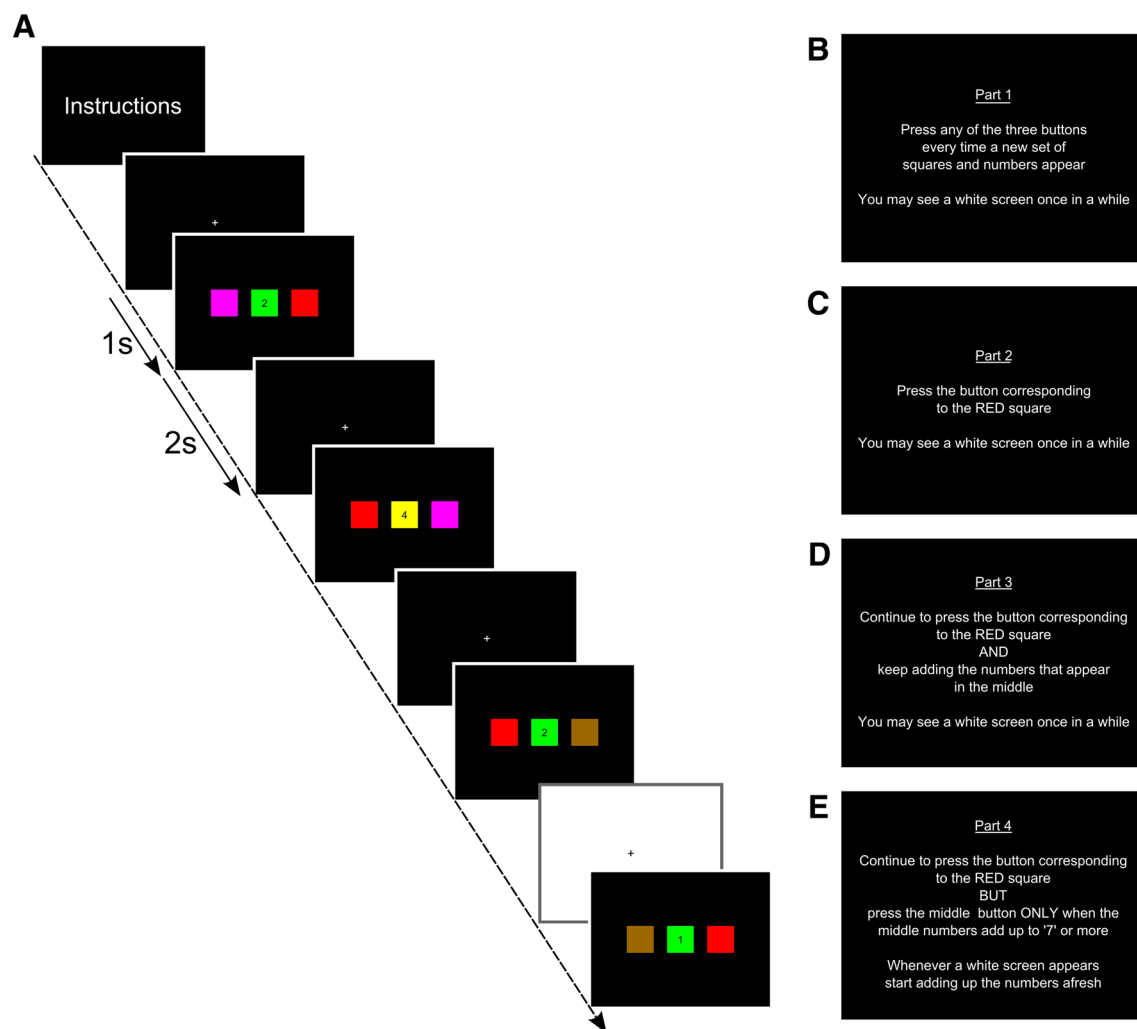
Experimental design

The fMRI experiment consisted of four task conditions in a blocked design pattern implemented using the E-Prime stimulus presentation software, version 1.0 (PST Inc, Philadelphia, USA, www.pstnet.com/) operating within the Integrated Functional Imaging System (IFIS–SA) (Invivo, Orlando, Florida, USA, www.invivocorp.com) running on Windows XP. Four blocks each of the four conditions were administered in a pseudo-random order with no two successive blocks being the same. Each block consisted of 10 trials (inter-trial interval, 3 s). Each trial began with the presentation of a white fixation cross on a black background for 1 s followed by a 2 s display of a set of three colored squares arranged horizontally in the middle with a single digit number (ranging from 1 to 4) superimposed on the center of the middle square. The square on either the left or the right side would be red, while the other two would be blue, green, yellow, magenta, or brown. The number displayed in the center of the display at each trial was in black color and subtended a visual angle of 2.8°

while the squares were three times taller. Subjects were required to respond to each trial by pressing one of the three buttons of a response pad with their index, middle, or ring fingers.

The four task conditions included a baseline (BL) task, a forced choice ongoing task (OT), a working memory (WM) task and a prospective memory (PM) task (Fig. 1). The baseline task condition involved a simple random choice task in which the subject was required to press any one of the three buttons as soon as a new set of squares and numbers appeared. The baseline condition was included in the experimental paradigm to provide a meaningful control condition for contrasting against the ongoing task which involved a forced choice task. Since this contrast is not the subject of the present manuscript, the related results are not reported herein. The ongoing task was a forced choice task in which the subject was instructed to press the button on the side (index or ring finger) corresponding to the red square. In the working memory task, subjects were instructed to add the numbers presented across successive trials in the center of the display in addition to performing the ongoing task, i.e., participants had to press the button corresponding to the red square while serially adding the numbers that appear on the screen. Performance in the working memory task was assessed by asking the subject to report the total during a 9 s query period at the end of each WM block. During this 9 s query period (three scans of 3 s each), the subject had three opportunities (one silent period lasting 1 s between each scan) for reporting the running total. The instruction slide during this query period reminded the subjects to wait for the silent period to report the total. The prospective memory task required subjects to make a specific response—press the middle (middle finger) button on reaching a target total of seven in the serial addition task while continuing to perform the forced choice ongoing task. Subjects were instructed to reset the counting process once they reached or crossed the total of seven or, alternatively when they saw the fixation cross displayed against a white background instead of the usual black background. The white background in the prospective memory blocks was presented immediately following a trial in which the target sum of seven was expected to have been reached or crossed. This was included as a requirement to reset the serial addition task periodically. This resetting is required for two reasons—(1) to allow multiple prospective memory trials within a block and (2) to avoid a compounding of errors resulting from carrying forward of errors from the previous prospective memory trial into a subsequent one and therefore rendering all prospective memory trials within a block uninterpretable. The number of appearances of the white screen was 2–3 in each of the blocks irrespective of the condition. In both PM and non-PM blocks, the white screen followed every occasion when

Fig. 1 The "endogenous-cue prospective memory" fMRI experimental design. **a** Timeline of a block; **b–e** instructions for the baseline (BL), ongoing (OT), working memory (WM), and the prospective memory (PM) tasks

the running total reached or crossed seven and hence the number of such appearances were approximately similar across blocks. This ensured that the timing of the white screens matched between the prospective memory and other conditions. As mentioned under the behavioral performance section of Results, the prospective memory accuracy of the whole sample was around 70 %, and therefore, 'resetting' without a valid prospective memory response upon observing the white screen was required following only a minority (30 %) of the prospective memory intention retrieval contexts. Moreover, 'resetting' the counting process was anyway required even after a valid prospective memory response, much alike the 'resetting' of counting of dollar notes mentioned under the real-life example in the Introduction section. It may also be contended that since the resetting, if at all, occurs after the endogenous-cue prospective memory retrieval, the timing of the BOLD responses related to 'resetting' is not expected to substantially overlap with that of the

endogenous-cue prospective memory retrieval. The intention maintenance and monitoring components of prospective memory are active during the ongoing task trials of the prospective memory blocks, while the cue detection, intention retrieval, and execution components are active during the prospective memory trials. Thus, each of the PM blocks in its entirety modeled the prospective memory condition.

The total time taken for the paradigm was 10 min 40 s. All participants were briefed about the task on the evening prior to the imaging session, when they practised a short four-block version of the task (one block for each condition). Each block in the fMRI experiment was preceded by the display of an instruction slide for 8 s.

Image acquisition

Magnetic resonance imaging (MRI) was performed on a Philips Achieva 3.0 T scanner using an 8-channel phased

array head coil. Head movements were minimized by applying a band over the forehead during the scanning procedure. Single-shot echo-planar images (EPI) were acquired at an in-plane resolution of 2×2 mm with axial, sequential, contiguous 6 mm slices using a SENSE 8 acceleration; TR/TE, 3,000 ms/35 ms; flip angle, 90°; EPI factor, 59. The default number of slices was 24 with a slice thickness of 6 mm with no inter-slice interval. The actual number of slices acquired was dictated by the size of the head/brain and this is of no consequence for the image analyses. The acquisition included 220 volumes and was preceded by two dummy volumes that were discarded. A high-resolution ($1 \times 1 \times 1$ mm voxel size) T1-weighted MRI volume data set of the whole brain was also obtained using the same head coil for each subject [Magnetization Prepared Rapid Gradient Echo (MP-RAGE sequence) with TR 8.2 ms, TE 3.8 ms, flip angle 8°, and sense factor 3.5].

Image analysis

Preprocessing of the EPI images and further analyses were performed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) running on MATLAB (MathWorks Inc, Natick, Maryland, USA, www.mathworks.com/) operating on Windows XP. Briefly, the functional images of each participant were realigned with the first image to reduce movement-related artifacts. The 'unwarp' tool of SPM8 was then employed to minimize the geometrical distortion at the air–tissue interfaces, which is compounded by movement (susceptibility-by-movement interaction). The images were then co-registered with the T1-weighted structural images using a 12 parameter affine transform and normalized to the standard MNI space using the ICBM152 template, following which they were smoothed by convolving with a Gaussian kernel of 9 mm full-width at half maximum (i.e., one and a half times the largest dimension of our voxel size, which is $2 \times 2 \times 6$ mm) (Mikl et al. 2008). The preprocessed and smoothed images were entered into a subject-level general linear model (GLM) analysis. The GLM included task-related regressors modeling the four task conditions as well as the instruction and working memory verbal reporting conditions. The SPM canonical hemodynamic response function was used as the bases function for convolving with the task regressors. A high-pass filter (HPF) with a cutoff of 320 s was used to minimize slow drifts. The HPF should ideally reduce slow drifts without affecting task-related BOLD signal variance. The experimental task in this study had a cycle period of 160 s. As an HPF of twice the cycle duration is recommended, the HPF was set at 320 s. Inspection of the power spectral density of the predicted BOLD response time course for the task regressors in the GLM suggested that the HPF used did not clip the expected BOLD response

peak. A restricted maximum likelihood algorithm was used for model estimation. Resulting contrast images for the PM-OT, WM-OT, and PM-WM 'T' contrasts were entered into a second-level, one-sample random effects (RFX) analysis. Variables that could have a confounding effect on executive function viz., age (Salthouse et al. 2004; Jurado and Rosselli 2007), gender (Kalkut et al. 2009; Mäntylä 2013), intellectual ability measured by WAIS-III matrix scores (Arffa 2007; Leeson et al. 2010) as well as task performance variables corresponding to the particular contrast (vide the respective tables) were entered as covariates in the RFX analyses. The resulting T maps were thresholded at $P < 0.05$ with topological false discovery rate (FDRp) correction for multiple comparisons (Chumbley et al. 2010; Chumbley and Friston 2009). This procedure controls the false discovery rate (FDR) of maxima or peaks. Unlike conventional FDR procedure which attempts to correct the P values for all voxels in the SPM treating them as a set of independent tests, the topological FDR implemented in SPM8 submits the P values for maxima to a FDR correction. This accounts for the nature of signal as a continuous function of the search space. Such a peak-wise FDR control has been proposed to be more sensitive than family-wise error (FWE) thresholding while having minimal costs in terms of false positives (Chumbley et al. 2010). Binary masks of BA10 (rostral prefrontal cortex), insula (13 & 47) and anterior cingulate (BA 24 & 32) were created using the WFU PickAtlas Tool Version 2.4 (http://fmri.wfubmc.edu/ software/PickAtlas) for region-of-interest (ROI) analysis and the resulting T maps were thresholded at $P < 0.05$ with topological FDR correction. It is reiterated herein that the above stringent topological peak threshold (FDRp < 0.05) was applied for carrying out analyses that examined the two major questions that were posed in this research, i.e., the second-level one-sample RFX analyses using the PM-OT and WM-OT 'T' contrasts.

The MNI coordinates of the suprathreshold voxels were converted into the Talairach space using a non-linear transform (Brett et al. 2002) and anatomical labels were retrieved by querying the Talairach Atlas Brain database through the Talairach Daemon Client (http://www.talairach.org; Lancaster et al. 2000).

Exploratory psychophysiological interactions (PPI) analysis

In the whole brain random effects analysis, the right rostral prefrontal cortex (rPFC) showed the most significant BOLD signal activations during the prospective memory task compared to the ongoing task. An exploratory psychophysiological interaction (PPI) analysis was performed in SPM8 to obtain preliminary trends regarding the

connectivity of this region with the rest of the brain during performance of the prospective memory task. For each subject, the BOLD signal time series was extracted from 9 mm spheres centered on the global maxima (right rPFC; MNI coordinates $x = 30$, $y = 46$, $z = 20$) of the whole brain T map for the PM-OT contrast. Extraction was performed using the eigenvariate extraction tool of SPM8 which extracts the principal eigenvariate of the BOLD responses from the voxels defined by the sphere. The BOLD time series was deconvolved with the SPM standard hemodynamic response function (HRF) to derive a representation of the underlying neuronal signal. This was then multiplied by the PM-OT task regressor and the resulting vector was reconvolved with the HRF to obtain a PPI vector. Following this a subject-level GLM analysis was set up to identify regions with interaction effects across the brain. The PPI vector along with the original BOLD time series and the task regressor convolved with HRF were entered as covariates. The model was estimated using a restricted maximum likelihood approach and the resulting statistical parametric maps were queried with appropriate T contrasts to generate summary contrast images for positive and negative interactions. These contrast images were entered into a second-level one-sample RFX analysis model with age, gender, WAIS-III matrix scores, and the prospective memory task accuracy scores as covariates. The same method was employed to generate PPI maps for the prospective memory condition with left dorsal anterior insula (MNI coordinates $x = -40$, $y = 14$, $z = 16$), the global maximum for the WM-OT contrast, as the seed region; for the working memory condition with left dorsal anterior insula (MNI coordinates $x = -40$, $y = 14$, $z = 16$), as the seed region; and for the working memory condition with right rPFC (MNI coordinates $x = 30$, $y = 46$, $z = 20$), as the seed region. For these exploratory analyses, the resulting T maps were thresholded at $P < 0.001$ (uncorrected), given the lower power of PPI analysis to detect task-related differences (O'Reilly et al. 2012). We chose to not include the PM-WM or the WM-PM contrasts for our exploratory PPI analyses, since, the unique cognitive process of this paradigm, i.e., the incremental updating of working memory, would get subtracted out with those contrasts.

Results

Behavioral performance in the task

The mean accuracies and latencies for each of the tasks are given in Fig. 2. The accuracy of ongoing task trials in the prospective memory blocks and the accuracy of the prospective memory trials were considered as indices for engagement in the prospective memory task. Correct responses for the prospective memory component of the prospective memory task condition, i.e., pressing the middle button when the sum of the serially added numbers equaled or exceeded 7, were scored. The mean performance accuracy score on the prospective memory trials for the 18 subjects was 0.69 (SD = 0.11). The mean ongoing task accuracy during the prospective memory blocks was 0.76 (SD = 0.11), in comparison to that during the ongoing task alone blocks (mean = 0.95, SD = 0.04). All subjects were adequately engaged in the serial addition task of the working memory condition as evidenced by a mean accuracy score of 0.91 (SD = 0.12) based on comparison of the reported block-end totals with the actual totals.

A repeated measures analysis of co-variance (ANCOVA) with age, gender, and WAIS-III matrix scores as covariates was performed to compare the accuracy and response latencies during the task conditions. The accuracy of the ongoing forced choice task (OT) during the prospective memory condition (mean = 0.76, SD = 0.11) was significantly lower compared to the working memory (mean = 0.93, SD = 0.04) and ongoing task (mean = 0.95, SD = 0.04) conditions [$F(2,51) = 35$, $P < 0.05$; $P < 0.001$, Bonferroni adjusted pair-wise comparisons]. The response latencies (ms) for the ongoing task trials were significantly greater during the prospective memory and working memory task conditions compared to the ongoing task and baseline task conditions (BL: mean = 628 ms, SD = 129; OT: mean = 709 ms, SD = 144; WM: mean = 1,035 ms, SD = 182; and PM: mean = 993 ms, SD = 109; $F(3,68) = 37$, $P < 0.05$; $P < 0.001$, Bonferroni adjusted pair-wise comparisons). On an average, there was a significant (72 %) lengthening of the response latencies of the ongoing trials within the prospective memory blocks compared to the ongoing trials of the ongoing task alone blocks. This reflects the cost function of the prospective memory intention on the ongoing task and is an indicator of engagement with the prospective memory task (Smith 2003; Marsh et al. 2006).

Random effects (RFX) analysis for whole brain

The brain regions that showed significant activations with the different SPM contrasts as well as the PPI contrasts (see below) are reorganized and reported according to previously described brain networks (Damoiseaux et al. 2006; Smith et al. 2009; Agosta et al. 2012; Bressler and Menon 2010) to which they belong (Tables 1, 2; S1–S4) for ease of understanding the possible functional significance of these activations.

The global maxima of PM-OT contrast in the one-sample RFX analysis (FDRp < 0.05) was localized to the right lateral rostral prefrontal cortex (MNI coordinates: $x = 30$, $y = 45$, $z = 16$) (Table 1). The other brain regions
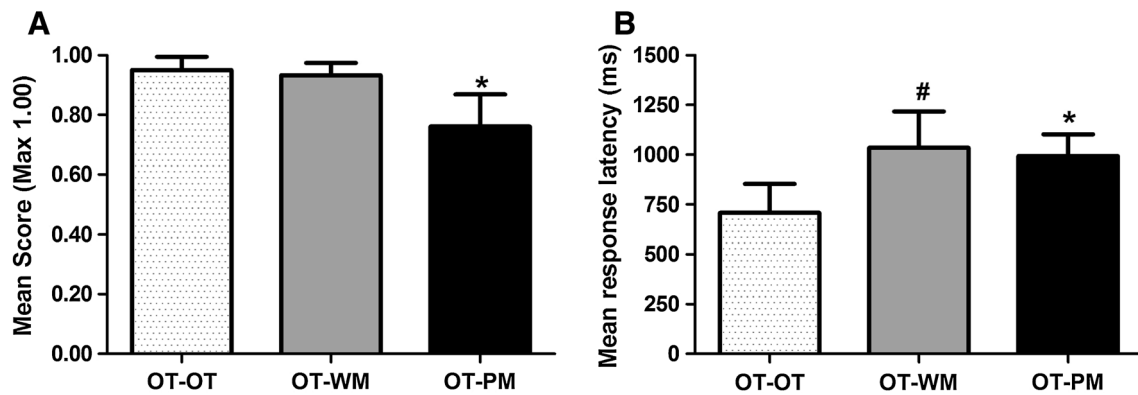
Fig. 2 Behavioral performance of the fMRI task. a Mean accuracy scores of the ongoing task component of trial responses for the ongoing (OT-OT), working memory (OT-WM), and "endogenous-cue prospective memory" (OT-PM) task blocks. OT accuracy score for PM block was significantly lower than the OT and WM blocks (*repeated measures ANOVA: $F(2,51) = 35$, $P < 0.05$; $P < 0.001$, Bonferroni adjusted pair-wise comparisons). b Mean response latencies for the ongoing trial responses for the ongoing (OT-OT), working memory (OT-WM), and "endogenous-cue prospective memory" (OT-PM) task blocks. OT response latencies for PM and WM blocks were significantly longer than the OT blocks (*,#Repeated Measures ANOVA: $F(3,68) = 37$, $P < 0.05$; $P < 0.001$, Bonferroni adjusted pair-wise comparisons)

that were involved in the performance of our 'endogenous-cue PM task' included those that have been previously described as belonging to the bilateral fronto-parietal (FP) network (including bilateral dorsolateral prefrontal cortex, bilateral inferior parietal lobules, left precuneus, left medial frontal gyrus, right precentral gyrus, right superior parietal lobule, and right middle temporal gyrus), the salience network (left anterior insula and right anterior fronto-insula) (Menon and Uddin 2010; Bressler and Menon 2010), dorsal salience network (right superior temporal gyrus) (Agosta et al. 2012; Nioche et al. 2009) as well as the cerebellar network (bilateral declive) (Damoiseaux et al. 2006; Smith et al. 2009; Agosta et al. 2012) (Fig. 3a; Table 1). The insular activations during PM-OT were maximum at $x = -30$, $y = 15$, $z = -4$, which borders the dorsal and ventral sub-divisions of the anterior insula (Deen et al. 2011). For the WM-OT contrast, the global maxima was localized to the left dorsal anterior insula ($x = -40$, $y = 14$, $z = 14$) (Deen et al. 2011) (Table 2). The WM-OT contrast (FDRp < 0.05) showed activations of the brain regions belonging to the salience network (bilateral anterior dorsal insula, left posterior insula, and left anterior cingulate gyrus) (Menon and Uddin 2010) in addition to activations of brain regions belonging to the dorsal salience network (right fusiform gyrus) (Agosta et al. 2012), bilateral fronto-parietal network and right claustrum (Fig. 3b; Table 2).

Since our experiment included a working memory task without the prospective memory intention, we hoped to answer the additional question whether prospective memory tasks with endogenous cues just reduces to working memory, or whether there is something more specific about 'endogenous-cue prospective memory' over and above

working memory. This was achieved by performing an additional exploratory PM-WM contrast. The PM-WM contrast did not show significant activations with topological FDR correction. However, at a voxel-wise FDR threshold (FDRv) of $P < 0.05$, it yielded a global maxima at the right rPFC ($x = 24$, $y = 55$, $z = 3$), which is spatially proximal to that of the PM-OT contrast noted above, with additional activations in widespread brain regions belonging to the bilateral FP network, dorsal and ventral salience networks (excluding the insula), bilateral claustrum and left cerebellar network (Fig. 4; Table S1).

Region-of-interest (ROI) analyses

We performed ROI analysis (at FDRp < 0.05) restricted to the bilateral masks of rostral prefrontal cortex (BA10), dorsal anterior insula (BA 13 & 47), and anterior cingulate (BA 24 & 32), to examine how the BOLD activations in these regions differ across the prospective memory and working memory conditions. On ROI analysis restricted to the BA10 mask, both prospective memory task (Fig. 5a) and working memory task (Fig. 5b) were associated with significantly greater BOLD signal in the lateral rPFC compared to the ongoing task; however, the prospective memory condition had bilateral and more extensive activations compared to only the left unilateral BA10 activations during the working memory condition (Fig. 5b). Further, the prospective memory task was associated with significant BOLD activations in lateral rPFC and deactivations in the medial rPFC on both sides (Fig. 6), similar to the earlier findings of Burgess et al. (2003). On ROI analysis restricted to the insula mask (BA 13 and 47), both prospective memory and working memory conditions were

Table 1 One-sample random effects analysis: endogenous-cue prospective memory (PM) versus ongoing task (OT) contrast in healthy subjects ($n = 18$)

Region	L/R	Brodmann area	T	x	y	z
Fronto-parietal network (FPN)[b,c]/central executive network (CEN)[3]						
Rostral prefrontal cortex[a]	R	10	19.18	30	45	16
Superior parietal lobule	R	7	18.83	32	−54	43
Middle frontal gyrus	L	6	17.12	−28	4	50
Precuneus	L	7	16.91	−18	−56	45
Inferior parietal lobule	R	40	15.41	40	−41	41
Inferior parietal lobule	L	40	14.68	−50	−35	40
Middle frontal gyrus	R	6	12.67	30	12	45
Middle temporal gyrus	R	39	12.22	32	−65	29
Inferior frontal gyrus	R	46	11.22	40	33	8
Precentral gyrus	R	9	10.43	32	6	35
Middle frontal gyrus	R	9	9.88	34	38	26
Medial frontal gyrus	L	9	8.31	−22	38	20
Central salience network (SN)[d]						
Insula (anterior; bordering dorsal/ventral sub-regions)	L	13	11.89	−30	15	−4
Inferior frontal gyrus (fronto-insula: anterior; bordering dorsal/ventral sub-regions)	R	47	8.95	32	19	−4
Other brain regions putatively involved in mediating salience-dorsal salience network[c,e]						
Superior temporal gyrus	R	41	7.03	44	−39	6
Cerebellar network (CN)						
Declive	L		9.51	−8	−79	−18
Declive	R		6.8	40	−65	−20

Age; gender; WAISIII matrix reasoning score; difference in accuracy of all trials (OT + PM) in PM condition and the OT trials in the OT condition and difference in response latencies of all trials (OT + PM) in the PM condition and OT trials in the OT condition are entered as covariates of no interest. Voxel-level maxima significant at $P < 0.05$, corrected for multiple comparisons by topological false discovery rate method, FDRp (height threshold $T = 6.64$, extent threshold $k = 0$ voxels) are reported. Coordinates are in Talairach space. The brain regions showing significant activations are organized under previously reported brain networks, of which these brain regions are constituent 'nodes', based on the Talairach co-ordinates of each voxel maxima

[a] Brodmann Area 10 labeled as superior/middle/medial frontal gyrus by Talairach Daemon has been relabeled as rostral prefrontal cortex.
[b] Damoiseaux et al. (2006); [c] Agosta et al. (2012); [d] Bressler and Menon (2010); [e] Nioche et al. (2009)

found to be associated with increased BOLD signal in the bilateral (L > R) dorsal anterior insula (Fig. 7a); the WM-OT contrast revealed left posterior insula activations as well (Fig. 7b). The ROI analysis restricted to the anterior cingulate mask (BA 24 and 32), however, revealed only a single cluster of increased activation during the prospective memory condition, but not during the working memory condition, in comparison to the ongoing task condition (Fig. 8).

Exploratory psychophysiological interactions (PPI) analyses

To explore how the right rostral prefrontal cortex (global maxima for PM-OT) interacts with other brain regions in the performance of the prospective memory task, we performed a PPI analysis, which revealed positive interactions with brain regions belonging to the right dorsal salience network, left ventral salience network, bilateral central salience network, bilateral FP network, bilateral cerebellum, and right claustrum ($P < 0.001$ uncorrected) (Fig. 9a; Table S3). Task-related negative interactions were also noted with left anterior cingulate cortex, left middle temporal gyrus, and left caudate head (Fig. 9e). PPI analysis during the working memory condition with right rostral prefrontal cortex as seed revealed positive interactions with brain regions belonging to the right central salience network, right dorsal salience network, bilateral ventral salience network, bilateral FP network, right lentiform nucleus, and bilateral cerebellar network ($P < 0.001$ uncorrected; Fig. 9d; Table S6); negative interactions were noted with left middle temporal gyrus, left anterior cingulate cortex, left angular gyrus, and left rostral prefrontal cortex (Fig. 9h).

For the WM-OT contrast, the left dorsal anterior insula (global maxima) showed extensive positive PPIs with brain regions belonging to the bilateral dorsal and ventral salience networks, the right central salience network (right

Table 2 One-sample random effects analysis: working memory (WM) versus ongoing task (OT) contrast in healthy subjects ($n = 18$)

Region	L/R	Brodmann area	T	x	y	z
Central salience network (SN)[1]						
Insula (dorsal anterior)	L	13	12.93	−40	14	14
Insula (posterior)	L	13	10.31	−50	−40	17
Insula (anterior; bordering dorsal/ventral sub-regions)	L	13	8.51	−46	14	−1
Cingulate gyrus (anterior)	L	32	8.19	−8	19	34
Insula (anterior; bordering dorsal/ventral sub-regions)	R	13	7.87	40	15	−2
Ventral salience network[c]/visual network[d]						
Fusiform gyrus	R	20	8.1	44	−24	−14
Fronto-parietal network (FPN)[c,e]/central executive network (CEN)[b]						
Medial frontal gyrus	L	6	12.41	−4	16	45
Medial frontal gyrus	L	6	11.29	−16	11	57
Superior frontal gyrus	R	6	9.5	12	9	59
Inferior parietal lobule	L	40	8.98	−46	−37	42
Middle frontal gyrus	L	6	8.66	−48	2	42
Rostral prefrontal cortex[a]	L	10	8.29	−30	47	14
Superior frontal gyrus	R	6	8.27	22	10	51
Middle frontal gyrus	L	6	8.22	−30	6	40
Superior frontal gyrus	R	6	8.15	24	12	53
Middle frontal gyrus	L	9	8.15	−36	40	27
Precentral gyrus	R	6	8.04	50	−4	35
Middle frontal gyrus	R	8	7.86	26	14	44
Superior frontal gyrus	R	6	7.84	22	9	55
Claustrum	R		8.02	30	21	1

Age; gender; WAISIII matrix reasoning score; difference in accuracy of OT trials in the WM condition and OT trials in the OT condition; and difference in response latencies of OT trials in the WM condition and OT trials in the OT condition are entered as covariates of no interest. Voxel-level maxima significant at $P < 0.05$, corrected for multiple comparisons by topological false discovery rate method, FDRp (height threshold $T = 3.93$, extent threshold $k = 0$ voxels) are reported. Coordinates are in Talairach space. The brain regions showing significant activations are organized under previously reported brain networks, of which these brain regions are constituent 'nodes', based on the Talairach co-ordinates of each voxel maxima

[a] Brodmann area 10 labeled as superior/middle/medial frontal gyrus by Talairach Daemon has been relabeled as rostral prefrontal cortex. [b] Bressler and Menon (2010); [c] Agosta et al. (2012); [d] Smith et al. (2009); [e] Damoiseaux et al. (2006)

anterior cingulate cortex), bilateral FP network, right hypothalamus, left thalamus, bilateral cerebellum, and right parahippocampal gyrus ($P < 0.001$ uncorrected) (Fig. 9b; Table S4); negative interactions were noted with right anterior cingulate cortex, left angular gyrus, left rostral prefrontal cortex, and left posterior cingulate cortex (Fig. 9f). PPI analysis during the prospective memory condition with left dorsal anterior insula as seed revealed positive interactions with brain regions belonging to bilateral FP network, left central salience network, left posterior insula, right posterior cingulate, right dorsal salience, and bilateral ventral salience network ($P < 0.001$ uncorrected; Fig. 9c; Table S5); negative interactions were noted with left anterior cingulate cortex, left middle temporal gyrus, and left superior temporal gyrus (Fig. 9g).

Thus, both prospective memory and working memory conditions involved positive PPIs of the right rostral prefrontal cortex with brain regions that are part of the central, dorsal, and ventral salience networks as well as the frontoparietal and cerebellar networks. However, it may be noted from Tables S3 and S6 that the PPIs of the right rostral prefrontal cortex during the prospective memory condition were restricted to the prefrontal regions of the fronto-parietal network, whereas during the working memory condition there were more extensive connections involving the frontal, temporal, and parietal regions of the fronto-parietal network. Similarly, the left dorsal anterior insula showed positive PPIs with the brain regions that constitute the central, dorsal, and ventral salience networks as well as the fronto-parietal network during both prospective memory and working memory conditions (Tables S4 and S5). As noted with the right rostral prefrontal cortex, the left dorsal anterior insula too showed more extensive PPIs involving the frontal, temporal, and parietal regions of the fronto-parietal network, in addition to other brain regions such as hypothalamus, thalamus, cerebellum, and parahippocampal gyrus during the working memory condition (Table S4). The prospective memory condition, however, was associated with more circumscribed PPIs of the left dorsal anterior insula with the prefrontal regions of the fronto-parietal network, apart from brain regions that constitute the salience networks (Table S5).

Discussion

In this study, we investigated the neural correlates of an 'endogenous-cue prospective memory paradigm' wherein incremental updating of working memory forms an integral part essential for intention retrieval. We found that, at the neural level, this prospective memory task showed maximum
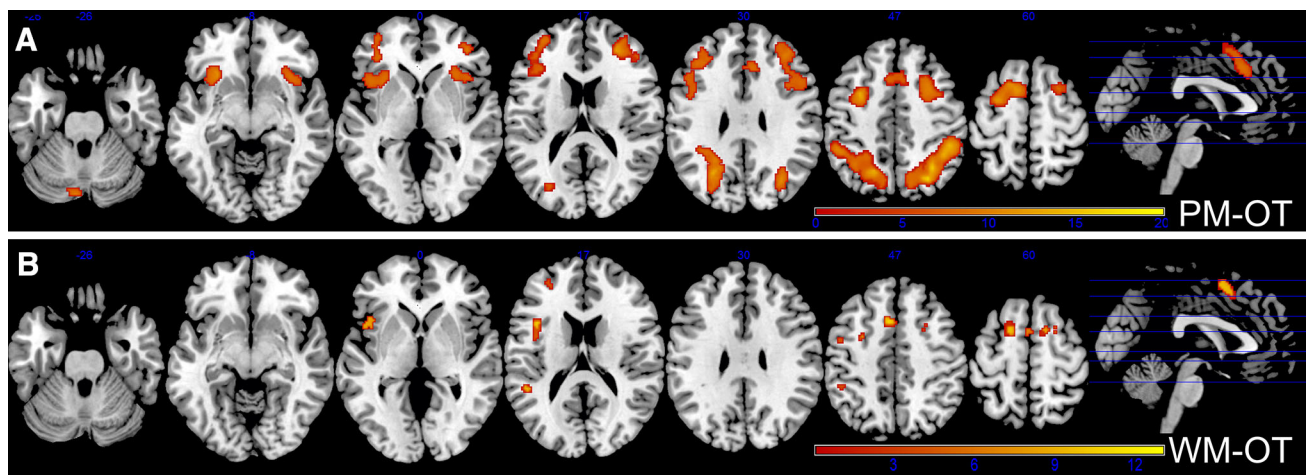
Fig. 3 Whole brain, one-sample random effects (RFX) analysis. **a** 'Endogenous-cue prospective memory' (PM) versus Ongoing task (OT) contrast; **b** Working memory (WM) versus OT contrast; Age; gender; WAIS-III matrix reasoning scores; and task performance variables corresponding to the particular contrast (see legends of Tables 1 and 2) were entered as covariates of no interest. T maps are thresholded at $P < 0.05$ with topological false discovery rate (FDRp)-based correction for multiple comparisons (height threshold $T = 6.64$ for PM-OT, 7.82 for WM-OT; extent threshold $k = 0$ voxels). Images as per neurological convention (image left is subject's left)

Fig. 4 Whole brain, one-sample random effects (RFX) analysis. Endogenous-cue prospective memory (PM) versus working memory (WM) contrast. Age; gender; WAIS-III matrix reasoning scores; and task performance variables corresponding to the PM-WM contrast (see legend of Table S1) were entered as covariates of no interest. T maps are thresholded at $P < 0.05$ with voxel-wise false discovery rate (FDRv)-based correction for multiple comparisons (height threshold $T = 3.56$; extent threshold $k = 0$ voxels). Images as per neurological convention (image left is subject's left)
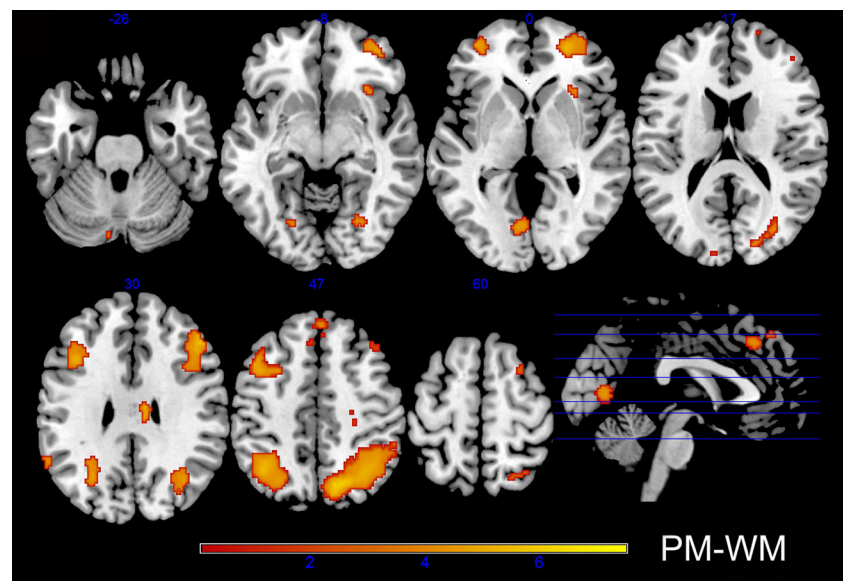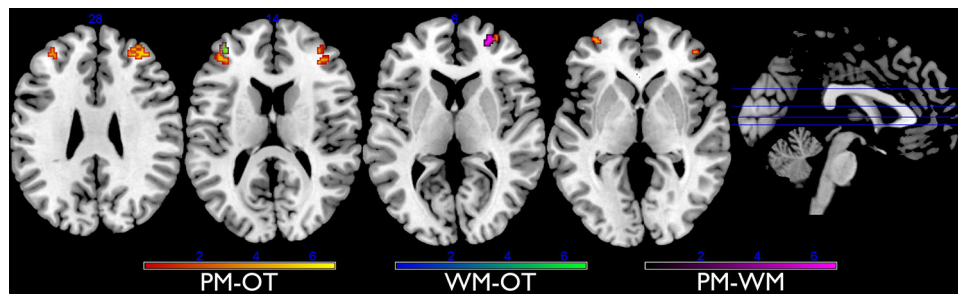
activation at the right rostral prefrontal cortex, with additional activations in brain regions as reported previously with other prospective memory tasks. Importantly, the robust activation of the dorsal anterior insula, which mediates the incremental updating of working memory that generates the intention retrieval context, differentiates this prospective memory task from other prospective memory sub-types.

Benoit et al. (2012) recently described the neural correlates of stimulus-oriented and stimulus-independent thinking using an endogenous-cue prospective memory task in which the prospective memory cues were encountered during the performance of "imagined" ongoing task. Though these stimuli for the ongoing task were

endogenous, the generation of the prospective memory cues was not dependent upon incremental updating of working memory. In fact, the subjects were required to memorize the prospective memory targets at the beginning of each prospective memory block; thus incremental updating of working memory was not required for the generation of the intention retrieval context, unlike for the paradigm used in our study. Therefore, the 'endogenous-cue prospective memory task' described in the present study constitutes a novel paradigm that requires, in addition to the ongoing task (OT) and an endogenous cue, an incremental updating of working memory, which generates the cue for the intention retrieval and execution.

Fig. 5 Region-of-interest analysis of rostral prefrontal cortex (BA10). Overlays of significant BOLD activations in the 'Endogenous-cue prospective memory' (PM) task versus ongoing task (OT) contrast (*red–yellow*), working memory (WM) versus OT contrast (*blue–green*) contrast and PM-WM contrast (*violet*). Age; gender; WAISIII matrix reasoning score; difference in accuracy of all trials (OT + PM) in PM condition and the OT trials in the OT condition; and difference in response latencies for all trials (OT + PM) in the PM condition and OT trials in the OT condition were entered as covariates of no interest. T maps are thresholded at $P < 0.05$ with topological false discovery rate (FDRp)-based correction for multiple comparisons (height threshold $T = 5.62$ for PM-OT, 5.54 for WM-OT, 5.89 for PM-WM; extent threshold $k = 0$ voxels). Images as per neurological convention (image left is subject's left)
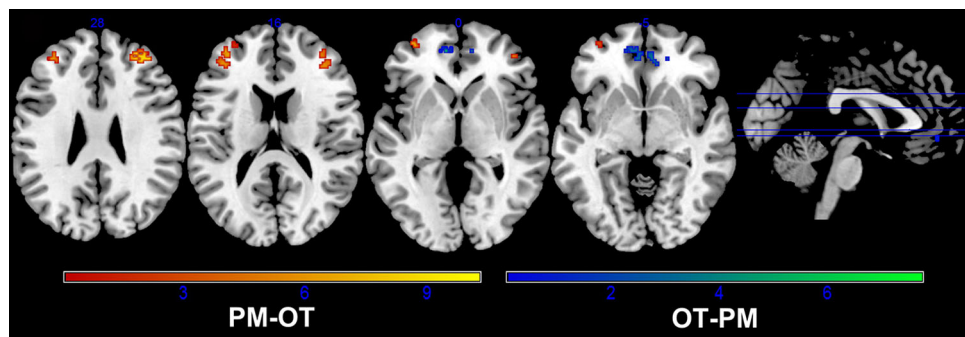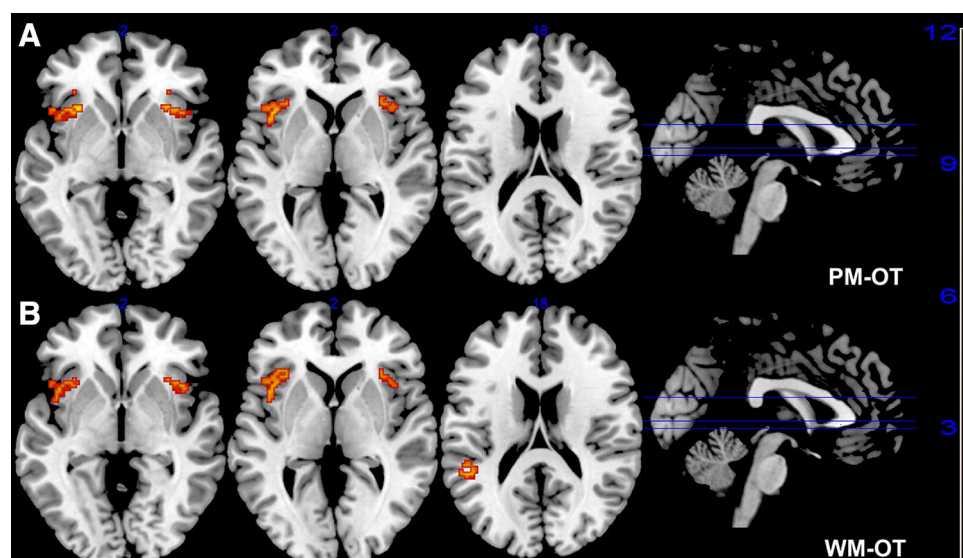

Fig. 6 Region-of-interest analysis of rostral prefrontal cortex (BA10). Overlays of significant BOLD activations in the PM-OT contrast (*red–yellow*) and OT-PM (*blue–green*) contrast. Age; gender; WAISIII matrix reasoning score; difference in accuracy of all trials (OT + PM) in PM condition and the OT trials in the OT condition; and difference in response latencies for all trials (OT + PM) in the PM condition and OT trials in the OT condition were entered as covariates of no interest. T maps are thresholded at $P < 0.05$ with topological false discovery rate (FDRp)-based correction for multiple comparisons (height threshold $T = 5.43$, extent threshold $k = 0$ voxels). Images as per neurological convention (image left is subject's left)

One-sample random effects analysis of the PM-OT contrast found that the global maxima was localized to the right rostral prefrontal cortex (BA10) (Fig. 3). ROI-based analysis of the BA10 confirmed the maximal right rostral prefrontal cortex activations during prospective memory when compared to both the ongoing task as well as working memory conditions (Fig. 5). The left rostral prefrontal cortex was also activated, along with other brain regions that belong to the fronto-parietal network. Additional activations were also found in the bilateral cerebellum and right superior temporal gyrus as described in many earlier studies (Kalpouzos et al. 2010; Gilbert et al. 2009; den Ouden et al. 2005; Hashimoto et al. 2011). The robust activation of BA10 as well as other fronto-parietal regions during the performance of our prospective memory task extends the findings from previous studies by demonstrating that, the rostral prefrontal cortex is maximally activated during an endogenous-cue prospective memory task requiring incremental updating of working memory, much like the previously described exogenous-cue (for review, see Burgess et al. 2011) and 'endogenous-cue' (Benoit et al. 2012) prospective memory tasks. The fronto-parietal brain regions constitute the seat of sustained and dynamic aspects of attention, which integrates bottom-up representations of perceptual features mediated by the parietal regions and top-down cognitive processes mediated by the prefrontal regions (Ptak 2012). Specifically, the rostral prefrontal cortex has been consistently shown to be the most crucial brain region that is responsible for the maintenance of intention in prospective memory tasks (Burgess et al. 2007). The PM-WM contrast (FDRv $P < 0.05$) revealed extensive regions that were more activated during the prospective memory task, predominantly the fronto-parietal regions, with the global maxima localized to the right rostral prefrontal cortex (Fig. 4; Table S1). This is indicative of the greater demands placed on the brain regions that constitute the fronto-parietal network by the prospective memory condition in comparison to the

Fig. 7 Region-of-interest analysis of Insula (BA 13 & 47). Overlays of significant BOLD activations in the 'Endogenous-cue prospective memory' (PM) task versus ongoing task (PM–OT) contrast (**a**), working memory versus OT (WM-OT) (**b**) (Note: there were no significant voxels in the insular region for the PM-WM contrast). Age; gender; WAIS-III matrix reasoning scores; and task performance variables corresponding to the particular contrast (vide legends of Tables 1 and 2) were entered as covariates of no interest. T maps are thresholded at $P < 0.05$ with topological false discovery rate (FDRp)-based correction for multiple comparisons (height threshold $T = 5.68$ for PM-OT, 5.62 for WM-OT; extent threshold $k = 0$ voxels). Images as per neurological convention (image left is subject's left)
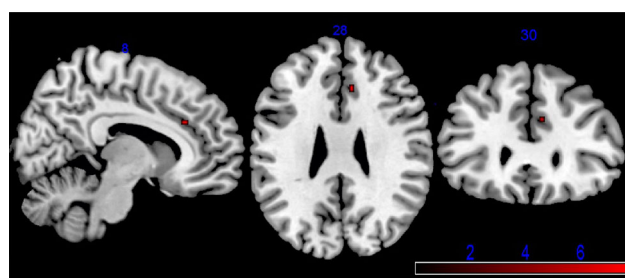

Fig. 8 Region-of-interest analysis of anterior cingulate (BA 24 & 32). Overlays of significant BOLD activations in the 'Endogenous-cue prospective memory' (PM) task versus Ongoing task (PM–OT) contrast (Note: there were no significant voxels in the anterior cingulate region for the WM-OT and PM-WM contrasts). Age; gender; WAIS-III matrix reasoning scores; and task performance variables corresponding to the particular contrast (vide legends of Tables 1, 2 and S1) were entered as covariates of no interest. T maps are thresholded at $P < 0.05$ with topological false discovery rate (FDRp)-based correction for multiple comparisons (height threshold $T = 7.06$ for PM-OT; extent threshold $k = 0$ voxels). Images as per neurological convention (image left is subject's left)

working memory condition. The findings of our ROI analysis using BA10 mask, provides further confirmatory evidence for a lateral-medial dissociation as proposed by Burgess et al. (2003) in the performance of prospective memory tasks (Fig. 6). Such a lateral-medial functional specialization of rostral prefrontal cortex has been suggested to support two distinctive cognitive processes viz. a "stimulus-oriented" (SO) state characterized by attention to the current sensory input and a "stimulus-independent" (SI) state in which the focus is on self-generated or self-maintained thought. According to this account, the rostral prefrontal cortex (BA10) plays the role of an "attentional gate" in switching between SO (medial rostral prefrontal cortex) and SI (lateral rostral prefrontal cortex) states (Burgess et al. 2007).

We then examined whether the 'endogenous-cue prospective memory task' with incremental updating of working memory described herein, uniquely activates any brain regions that have not been reported hitherto with other prospective memory paradigms, particularly the brain regions that constitute the salience network (viz., dorsal anterior insula and anterior cingulate). Interestingly, in keeping with our a priori hypothesis, the performance of the prospective memory task was associated with activations in the bilateral anterior insula which forms a part of the central salience network (Menon and Uddin 2010; Agosta et al. 2012). The anterior insula activations that were noted during the performance of the 'endogenous-cue prospective memory task' differentiates it from previous exogenous and endogenous-cue prospective memory tasks without the additional incremental working memory updating process described above (e.g., Burgess et al. 2001, 2003; Okuda et al. 2007, 1998; Hashimoto et al. 2011; Kalpouzos et al. 2010; den Ouden et al. 2005; Gilbert et al. 2009). A few studies have reported insular activations at an uncorrected statistical threshold (e.g., Hashimoto et al.
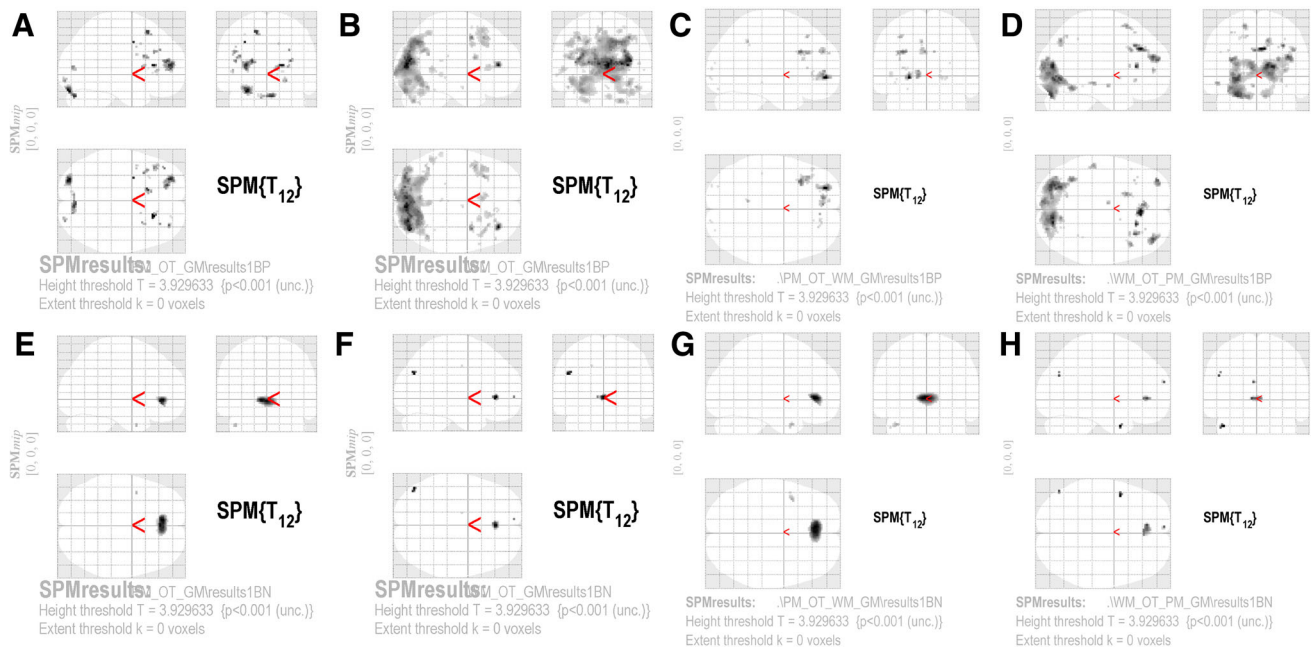
Fig. 9 Psychophysiological interactions assessed for 9 mm spherical VOIs centered at the global maximum from the RFX analysis for 'endogenous-cue prospective memory' (PM) versus Ongoing Task (OT) [MNI co-ordinates, $x = 30$, $y = 46$, $z = 20$; right rostral prefrontal cortex] and working memory (WM) versus OT contrasts [MNI co-ordinates, $x = -40$, $y = 14$, $z = 16$; left anterior insula]. Brain regions with BOLD signal activity positively (**a**, **d**) and negatively (**e**, **h**) correlated with right rostral prefrontal cortex during the PM condition and WM condition, respectively; Brain regions with *bold* signal activity positively (**b**, **c**) and negatively (**f**, **g**) correlated with left anterior insula during the WM condition and PM condition, respectively. Age; gender; WAIS-III matrix reasoning scores; and task performance variables corresponding to the particular contrast (vide legends of Tables 4, 5) were entered as covariates of no interest. T maps thresholded at $P < 0.001$ (uncorrected, height threshold $T = 3.93$, extent threshold $= 0$ voxels). Images as per neurological convention (image left is subject's left)

2011; Gilbert et al. 2009), indicating that anterior insula activations, though less pronounced, does occur with prospective memory tasks that do not involve incremental updating of working memory. Since no previous study using exogenous or endogenous prospective memory cues have reported anterior insula activations after stringent correction for multiple comparisons, it can be inferred that robust anterior insula activations are a unique feature of our endogenous-cue prospective memory task involving incremental updating of working memory. This is further substantiated by the observation of the global maxima of activations during the working memory task in the dorsal anterior insula (see below). Thus, the finding of additional activations of the dorsal anterior insula, which mediates the incremental updating of working memory that generates the intention retrieval context, provides compelling evidence that the 'endogenous-cue prospective memory task' with incremental working memory updating described herein is distinguishable from other prospective memory tasks cited above.

Finally, the working memory process that generated the intention retrieval context in our prospective memory task was modeled in a separate working memory condition as described earlier. For this WM-OT contrast, activations of the bilateral dorsal anterior and left anterior cingulate gyrus that constitute the central salience network, along with activations of the posterior insula, right fusiform (ventral salience) gyrus, bilateral fronto-parietal regions, and right claustrum were noted, with the global maxima localized to the left dorsal anterior insula (Table 2). Moreover, ROI analysis of the insula revealed bilateral dorsal anterior activations associated with both prospective memory and working memory tasks in comparison to the ongoing task condition (Fig. 7). ROI analysis of the anterior cingulate revealed a single cluster of increased activations during the prospective memory task but not during the working memory task, in comparison to the ongoing task condition (Fig. 8). It is amply evident from the above that activations in brain regions that constitute the salience network, especially, the dorsal anterior insula, underlies the incremental updating of working memory that distinguishes our prospective memory task from other types of prospective memory tasks.

The results of the exploratory PPI analysis reveal the interactions of right rostral prefrontal cortex (global maxima from the PM-OT whole brain random effects analysis) and the left dorsal anterior insula (global maxima from the WM-OT whole brain random effects analysis) with other

brain regions during both prospective memory and working memory conditions. Both the prospective memory and working memory conditions involved interactions between the right rostral prefrontal cortex and left dorsal anterior insula with brain regions that are part of the salience networks, fronto-parietal network, and cerebellar network. However, the two conditions differed in the extent of connectivity of the above regions with brain areas that are part of the fronto-parietal network. The prospective memory condition was associated with more circumscribed connections of the above seed regions with the prefrontal regions of the fronto-parietal network. This indicates that the prospective memory condition is mediated predominantly by the prefrontal brain regions interacting with the brain regions that comprise the salience networks. The working memory condition was associated with more extensive connections involving the prefrontal, temporal, and parietal brain regions of the fronto-parietal network, apart from connections with other brain regions (see Tables S4 and S6). This indicates the demands placed on these brain regions for the performance of a working memory condition involving serial addition of numbers over ten successive trials, while performing the ongoing task. It may be recalled that, in the prospective memory condition, this serial addition was truncated upon reaching a sum of 7, at which point the subject was expected to execute the prospective memory intention. Together with the results of the one-sample random effects analyses, it may be inferred that prospective memory involves participation of prefrontal brain regions interacting with the brain regions that are part of the salience networks, as well as cerebellum and claustrum, with the maximum activation being localized to the right rostral prefrontal cortex. Working memory on the other hand, involves participation of more extensive brain regions belonging to the salience networks, fronto-parietal networks, hypothalamus, thalamus, cerebellum, and parahippocampal gyrus, with the maximum activations being localized to the left dorsal anterior insula.

The anterior cingulate cortex, posited to be an important node in the central salience network, along with the dorsal anterior insula (Menon and Uddin 2010), was found to have both positive as well as negative PPIs with the right rostral prefrontal cortex and left dorsal anterior insula in both the conditions. However, the regions in the anterior cingulate cortices showing positive and negative PPIs with both seed regions during the prospective memory and working memory conditions are spatially distinct (see Tables S4–S6), indicating that there may be functional sub-divisions within the anterior cingulate cortex. These reciprocal bidirectional interactions might enable the detection of salient stimuli by the dorsal anterior insula and the modulation of responses in the sensorimotor and association cortices by the anterior cingulate cortex (Menon and Uddin 2010).

The insula is a multimodal integration region that functions as an interface between external information and internal motivation states (Deen et al. 2011). Of the three insular sub-regions (dorsal anterior, ventral anterior, and posterior) (Deen et al. 2011; Kelly et al. 2012; Chang et al. 2013), the dorsal anterior insula is considered as a critical functional hub in the human brain (Uddin et al. 2014). Together with anterior cingulate, it critically mediates detection of salient stimuli through switching between the fronto-parietal and the default-mode networks (Greicius et al. 2003). Further, it is involved in initiation of attentional control signals (Uddin et al. 2014) that recruit brain networks mediating task-related information processing such as attentional, working memory, and other higher order cognitive processes (Menon and Uddin 2010). In view of its role in coordinating other large-scale brain networks, the dorsal anterior insula is considered as a 'causal outflow hub' (Uddin et al. 2014, 2011). Therefore, the robust dorsal anterior insula activations associated with our 'endogenous-cue prospective memory task' indicates the greater load on the salience network for sustaining the incremental working memory updating process that generates the intention retrieval context. Coupled with this, the observation of widespread activation of the dorsal anterior insula and other brain regions that constitute the salience network during the working memory task, confirms the critical role of these regions in the performance of tasks that involve sustained cognitive operations involving multiple processes mediated by different brain networks. The findings of the exploratory PPI analyses discussed above provide further evidence for the role played by interactions of the dorsal anterior insula with the rostral prefrontal cortex in the performance of our endogenous prospective memory task involving incremental updating of working memory.

The subjects who participated in the study were adequately engaged in the experimental paradigm as revealed by high ongoing task accuracy during the ongoing task condition (mean = 0.95) and high working memory accuracy during the working memory condition (mean = 0.91). The comparatively lower ongoing task accuracy scores during the prospective memory blocks (mean = 0.76) and prospective memory accuracy scores (mean = 0.69) reflect the cost function of the more cognitively demanding prospective memory task in this experiment that involved incremental updating of working memory for generation of the intention retrieval context. The PM-OT and WM-OT contrasts yielded significant activations at the topological FDRp ($P < 0.05$)-corrected threshold, with the global maxima at the right rostral prefrontal cortex and left dorsal anterior insula, respectively. These findings provide robust evidence for the role of the above brain regions in prospective memory and working memory, respectively. The PM-WM contrast yielded significant activations only at the

voxel-level FDRv ($P < 0.05$)-corrected threshold, which is still a stringent method of correction for multiple comparisons at the voxel level. Moreover, the global maxima of the PM-WM contrast was localized to the same region in the right rostral prefrontal cortex as in the PM-OT contrast, thus confirming the critical role of right rostral prefrontal cortex in prospective memory. A potential methodological limitation of the study may be the absence of an endogenous-cue prospective memory task that does not involve incremental updating of working memory within the same experimental session that could have permitted comparisons within the same study. Administering two types of prospective memory tasks, which are similar in all aspects other than the process of incremental working memory updating in a pseudorandom order within the same session could be confusing for the participants. This might impact the behavioral performance during both the prospective memory conditions, and therefore, we decided not to include such a task within the same study. However, this indeed is an issue that we hope to address in future studies.

Conclusion

This study provides compelling evidence for the critical role of rostral prefrontal cortex in endogenous-cue prospective memory tasks. The results of the study also provide convincing evidence for the role of the dorsal anterior insula in mediating incremental updating of working memory that generates the intentional retrieval context in the above prospective memory task. This robust activation of the dorsal anterior insula differentiates our 'endogenous-cue prospective memory task with incremental updating of working memory' from other endogenous—(e.g., Benoit et al. 2012) as well as exogenous—(e.g., Brewer et al. 2011) cue prospective memory tasks. Finally, the prospective memory task that we describe herein may be used universally across cultures in different neuropsychiatric populations, given the fact that it is culture free and language independent.

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