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The role of the rostral frontal cortex (area 10) in prospective memory: a lateral versus medial dissociation

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Abstract

Using the $H_2{}^{15}O$ PET method, we investigated whether previous findings of regional cerebral blood flow (rCBF) changes in the polar and superior rostral aspects of the frontal lobes (principally Brodmann's area (BA) 10) during prospective memory (PM) paradigms (i.e. those involving carrying out an intended action after a delay) can be attributed merely to the greater difficulty of such tasks over the baseline conditions typically employed. Three different tasks were administered under four conditions: baseline simple RT; attention-demanding ongoing task only; ongoing task plus a delayed intention (unpracticed); ongoing task plus delayed intention (practiced). Under prospective memory conditions, we found significant rCBF decreases in the superior medial aspects of the rostral prefrontal cortex (BA 10) relative to the baseline or ongoing task only conditions. However more lateral aspects of area 10 (plus the medio-dorsal thalamus) showed the opposite pattern, with rCBF increases in the prospective memory conditions relative to the other conditions. These patterns were broadly replicated over all three tasks. Since both the medial and lateral rostral regions showed: (a) instances where rCBF was lower during a more effortful condition (as estimated by increased RTs and error rates) than in a less effortful one; and (b) there was no correlation between rCBF and RT durations or number of errors in these regions, a simple task difficulty explanation of the rCBF changes in the rostral aspects of the frontal lobes during prospective memory tasks is rejected. Instead, the favoured explanation concentrates upon the particular processing demands made by these situations irrespective of the precise stimuli used or the exact nature of the intention. Moreover, the results suggest different roles for medial and lateral rostral prefrontal cortex, with the former involved in suppressing internally-generated thought, and the latter in maintaining it.

Keywords: Executive function; Frontal lobes; Delayed intention; Frontal pole

1. Introduction

"Prospective memory" (PM) is the field of enquiry concerned with how people create, maintain and execute intended actions after a delay period ("delayed intentions"). For most commentators this function is not supported by a single construct (e.g. [10,23,33,37,50,52]) and there are many different types of situations that involve prospective memory [14]. However the cardinal features of a prospective memory situation are shown in Table 1.

The study of the cognitive neuroscience of prospective memory is currently in its infancy. Nevertheless, a number of recent studies using different methodologies have suggested that processes supported by the fronto-polar and superior rostral aspects of the frontal lobes (approximating Brodmann's area (BA) 10) play a particularly important role in this function. A more precise characterisation of the role that this region plays is however currently hindered by one possibility which would compromise the utility of these findings for theorising. The present study seeks to investigate this possibility. We will first describe the evidence, and then outline the potential confound.

In a previous study, Burgess et al. [4] investigated regional cerebral blood flow changes in eight participants performing four different tasks, each under three conditions. The first condition (baseline) was subject-paced, and consisted of making judgements about two objects appearing together (e.g. which of two digits is the largest, or which of two letters comes nearer the start of the alphabet). The second condition consisted of the baseline task, but subjects were also told that if a particular combination of stimuli appeared (e.g. two vowels, two even numbers) they were to respond in

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Table 1
Features of a typical situation involving prospective memory

1	There is an intention, or multiple intentions [30] to act (or in some circumstances, to withhold a routine act)
2	The act cannot be performed immediately
3	The intention is to perform the act in a particular circumstance (the "retrieval context" [15]). In event-based studies, the retrieval context is signalled by a cue (the "intention cue")
4	The delay period between creating the intention and occurrence of the appropriate time to act (the "retention interval") is filled with activity known as the "ongoing task" [15]
5	Performance of the ongoing task prevents continuous, conscious rehearsal of the intention over the entire delay period. Typically this is because the activity is too demanding of attentional resources, or the delay period is too long
6	The intention cue (or retrieval context) does not interfere with, or directly interrupt, performance of the foreground task. Intention enactment is therefore self-initiated [24,49]
7	In most situations involving prospective memory no immediate feedback is given to the participant regarding errors

a different way (press a particular key combination). However in this condition ("expectation") none of these stimuli actually appeared. In the third condition participants were given the same instructions and stimuli as in the first, except that the expected PM stimuli did occur (after a delay, and on 20% of trials), and participants had the chance to respond to them ("execution" condition). In the terminology of prospective memory researchers, the last two conditions were "prospective memory" (PM) conditions in that they involved a delayed intention, and had the characteristics outlined in Table 1.

Burgess et al. [4] considered the rCBF changes between conditions that were common across the four tasks. Relative to the baseline condition, rCBF increases were seen in the frontal pole (BA 10) bilaterally, right DLPFC (BA 45/46) and right inferior parietal regions (BA 7, 19, 39, 40), precuneus, plus decreases in left fronto-temporal regions (BA 38, 47 and insula) when the participants were expecting to see a stimulus, even though it did not occur. Further increases were seen in the thalamus when the intention cues were seen and acted upon, with a corresponding decrease in right DLPFC. It was concluded that at least some of the rCBF changes in the expectation condition were most likely associated with intention maintenance, with those in the execution condition associated with recognising and responding to prospective memory cues.

The brain region regarded as especially significant as regards intention maintenance was BA 10, on the grounds of two previous studies. In the first [43] participants were taught a set of target nouns before scanning began. During scanning they were required to repeat verbally sets of five nouns that were presented to them. Occasionally one of these was one of the pre-learnt targets, and the participant was required to respond to them by tapping with their left hand. The contrast condition consisted of word string repetition alone. Okuda et al.'s [43] results implicated a number of frontal regions, including the right dorsolateral, ventrolateral (BA 8, 9, 47) and midline medial cortices (BA 8), and the anterior cingulate gyrus, plus the left parahippocampal gyrus. Most significantly for cross-study comparisons, they also implicated the left frontal pole (BA 10) in prospective memory (see also [42]).

The second supporting study was a human group lesion study [3] which showed that subjects whose lesions involved the medial anterior and polar regions of the left frontal lobe (principally BA 10) showed isolated problems with carrying out intended actions after a filled retention interval (see also [3] for details of single-case human lesion studies). Thus there seemed to be both within- and cross-method support for a role of BA 10 in prospective memory functions. Furthermore, the Burgess et al. [4] study suggested that this role was material- and stimulus non-specific, and probably involved more with maintenance rather than execution of the delayed intention.

However one possible explanation for the Burgess et al. [4] findings is that the activations seen in the expectation condition could be due to task difficulty or increased stimulus processing demands rather than anything to do with delayed intentions per se. This argument is given weight by recent findings of haemodynamic changes in fronto-polar regions associated with performance improvements in a variety of types of task [27,56]. One conception of what happens in a typical PM situation (see Table 1) is that the extra demand to recognise a PM cue might require the stimuli to be processed to a greater semantic "depth". Moreover it is plausible that compared with the ongoing task alone, giving a subject an additional (PM) instruction might encourage subjects to adopt a more cautious attitude to the stimuli or concentrate more closely on the task in general. These putative explanations sit in direct competition with the view of the BA 10 involvement in PM as non-specific to particular materials or stimuli, and its engagement in situations involving a delayed intention.

Certainly they are prima facie explanations for the other rCBF changes seen in Okuda et al. [43] and Burgess et al. [4]. Thus there are many functional imaging studies of a wide range of attention-demanding tasks that were not designed to have a delayed intention component. Most implicate right dorsolateral prefrontal cortex (DLPFC) (typically Brodmann's area (BA) 46) and right parietal (typically BA 40) regions (e.g. [9,16,28,35]). A regular but less consistent finding is the involvement of the anterior cingulate (e.g. [9,55]). In general the findings do not seem sensitive to the exact nature of the task, with these regions variously implicated in performance of a range of tasks from very simple vigilance ones [35] to those requiring considerable mental effort and stimulus processing such as rapid visual information processing [10] or the continuous performance test [28,55]. Considering the results common to the attention tasks together with those that are common to the PM paradigms, the only consistent feature that appears in the PM paradigms and not in the attention ones is the left frontal polar (BA 10) involvement. This is not a region that is generally associated with attention (see [8] for review) but appeared in both PET prospective memory studies. Thus it seems plausible that BA 10 involvement in PM tasks is not an artefact of the attentional demands made by increased stimulus processing or a consequence of the participants' response to task difficulty. However the hypothesis is certainly worthy of examination. It is doubtful whether such an explanation could be formally disproven. However we can at least determine whether the evidence is consistent with such a view.

Accordingly, this investigation involves two steps. The first is to contrast a set of simple baseline tasks that require basic attention to stimuli but no deep semantic or categorical processing of them, with a set of attention-demanding tasks that do require deep categorical processing. These attention-demanding tasks are (as a consequence) also more "difficult" in the accepted behavioural sense of inducing longer RTs and higher proportions of error. If the BA 10 rCBF changes previously found reflected changes in depth of stimulus processing, we might expect changes with this contrast. A second way of addressing the task difficulty argument is to examine rCBF changes within PM conditions as the task becomes easier for the subject with practice. If no BA 10 rCBF changes occur despite changes in RT and error rates, the result would favour a stimulus-independent processing account. (There are at least two definitions of "stimulus-independent processing". The first refers to thought not linked to the subject's current experimental situation, e.g. daydreaming [39]; the second refers to thought about a stimulus or potential response in the absence of it, as might occur for instance when one is consciously maintaining a particular thought in the presence of distracting stimuli. In the present context we use this second definition.)

2. Method

2.1. Experimental design

Three different types of tasks were administered to each participant: letter, number and picture processing. The logic of the design is to examine activations across them and therefore eliminate task-specific results which are of less interest to the present study (see e.g. [4,21]). We call this method "multiple task averaging". Each task was administered under three conditions. First, a baseline reaction time condition where participants made motor responses as fast as they could whenever stimuli on the screen changed (which was always 300 ms after their last response) (henceforth referred to as "baseline"). Second, an attention condition where participants performed a simple cognitive task that required continuous cognitive control ("ongoing task"). Third, two identical blocks of a condition involving the realisation of a delayed intention distinguished from each other only by the order in which they appeared ("PM1" and "PM 2"). The attention-demanding ongoing task was therefore similar to the baseline task except for the attention component, and the prospective memory conditions were identical to the ongoing ones except there was an additional requirement to execute a delayed intention.

The method of making a response was the same across all tasks, and all tasks were subject-paced with a 300 ms blank screen between trials. Subjects were asked to work as fast as they could in the both the baseline and ongoing task conditions without making mistakes. In the prospective memory conditions the instructions were slightly different. Pilot studies had shown that it was not uncommon once the delayed intention instruction was added to the ongoing task, for subjects to then treat the ongoing task as relatively unimportant, consequently showing much increased reaction times (RTs). The adoption of such a strategy could potentially violate characteristic 5 (see Table 1), and consequently reduce the construct validity of the task. We attempted to prevent the adoption of this strategy in the following way. In the PM conditions, we told participants that they would be given 20 pence (sterling) for each time they correctly responded to a PM stimulus. However we also said that they would only be awarded this money if their work-rates to the other stimuli were as fast as other students we had tested (no further information was given).

In the PM conditions, the delay interval between the start of the ongoing task and the appearance of the first PM stimulus was 30 s. Once the PM stimuli started to be presented, they constituted 20% of trials, with the interval between (i.e. the number of interleaved ongoing task trials) varied pseudo-randomly around an average of four trials. Presentation of these conditions was counterbalanced across participants, with the constraints that all four trials of any one type were presented in a blocked fashion. The novel prospective memory condition was identical to the practised prospective memory condition except that it always appeared first. RTs in all conditions were recorded.

2.2. Description of individual tasks

2.2.1. Number processing

Stimuli were presented on a 15 in. CRT monitor positioned approximately 60 cm from the subjects' eyes. In the baseline condition participants were presented with pairs of digits (from the range 1–9), and they just had to press one of two buttons as fast as they could whenever a new set of stimuli appeared. They were asked to make their responses on alternate response buttons, using the appropriate finger for each (forefinger for the left-hand key, middle finger for the right). In the ongoing task condition, participants decided whether the higher number was on the left- or right-hand side of the screen and pressed the response key on the same side (left or right) as this number (no ties were given). The PM conditions were identical to those of the ongoing task, except participants were told to press both response buttons together if two even numbers appeared together.

2.2.2. *Letter processing*

In the baseline condition participants were presented with pairs of capital letters. The participant pressed a response button as fast as they could in response to any change on the screen, using alternate fingers/keys as above. In the attention-demanding ongoing task condition, participants were presented with pairs of capital letters. The pairs were never identical, and were always between 11 and 16 letters apart in the alphabet (average distance = 13). Participants had to decide which letter (i.e. left- or right-hand side of the screen) came nearer the start of the alphabet, and press the corresponding L/R response key. The PM conditions were identical to the ongoing one except that the participants were additionally required to press both response buttons together if both letters on the same trial were vowels.

2.2.3. *Picture processing*

In all conditions participants were presented with a 4 by 6 grid containing two black circles. The position of the circles on the grid varied. In the baseline condition participants pressed a response button whenever they saw a picture appear on the screen using alternate response buttons as above. In the ongoing task, if the position of the two circles, relative to one another, was horizontal or vertical, then the participant was instructed to press the right response button. If the position of the two circles relative to one another was diagonal, the participants were instructed to press the left response button. The PM conditions were identical to the ongoing task except that they were additionally required to press both buttons together if both circles were in the middle two rows of the grid, regardless of their orientation.

2.3. *Subjects*

The subjects were nine men, mean age 30.0 years (S.D. = 7.14) who had no history of neurological disorders. All wrote with their right hands, were physically fit and none was taking medication. Written informed consent was obtained prior to the study. The study was approved by the local hospital ethics committee and the Administration of Radiation Safety Advisory Committee (UK).

2.4. *Data acquisition*

All subjects underwent both PET and MRI scanning on the same day. A Siemens VISION (Siemens, Erlangen) operating at $2.0T$ was used to acquire axial T_1 weighted structural images for anatomical coregistration. PET scans were performed with an ECAT EXACT HR+ scanning system (CTI Siemens, Knoxville, TN) PET in high sensitivity 3D mode with septa retracted. A venous cannula to administer the tracer was inserted in the antecubital fossa vein. Approximately 350 Mbq of $H_2{}^{15}O$ in 3 ml of normal saline were loaded into intravenous tubing and flushed into subjects over 20 s at a rate of 10 ml/min by an automatic pump. After a delay of approximately 35 s, a rise in counts could be detected in the head that peaked 30–40 s later (depending on individual circulation time). The data were acquired in one 90 s frame, beginning 5 s before the rising phase of the head curve. Images were reconstructed by filtered back projection (Hanning filter, cut off frequency 0.5 cycles per pixel) into 63 image planes (separation 2.4 mm) and into a 128 × 128-pixel image matrix (pixel size 2.1 mm). Twelve scans were collected over 96 min with an 8 min interval between scans during which the task instructions were given.

2.5. *Method of statistical analysis*

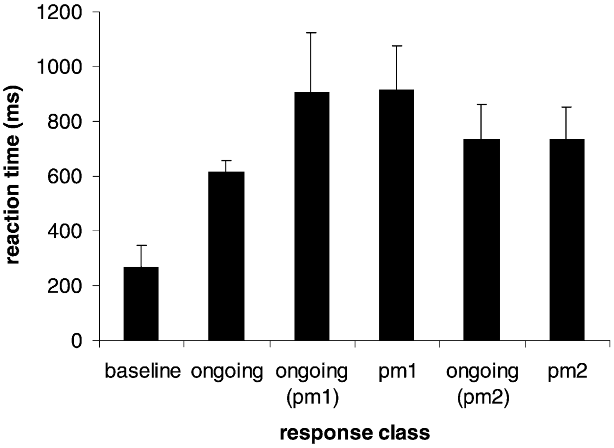
Functional imaging analysis used the technique of statistical parametric mapping implemented in SPM97 (Wellcome Department of Cognitive Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm) with a random effects design. For each subject, the set of 12 PET scans was automatically realigned and then stereotactically normalised [18] into the space of Talairach and Tournoux [58]. The scans were then smoothed using a Gaussian kernal of 12 mm full-width half maximum.

The analysis of functional imaging data entails the creation of statistical parametric maps that represent a statistical assessment of condition-specific effects hypothesised by the experimenter [20]. The effects of global changes in blood flow were modelled as a confound using a subject-specific analysis of variance (ANOVA) [19]. Areas of significant change in brain activity were specified by appropriately weighted linear contrasts of the condition specific effects and determined using the t-statistic on a voxel by voxel basis. We created the relevant SPM [t] for each comparison of conditions, which was then transformed into an SPM [Z]. Clusters of activated voxels were characterised in terms of their peak height and spatial extent conjointly.

3. Results

3.1. *Behavioural results*

Data was collapsed across tasks. There was a main effect of condition upon reaction times (RTs) ($F = 79.89$, d.f. = 3, 78, $P = 0.0001$). Unsurprisingly, post hoc contrasts showed quicker RTs in the baseline task than all other conditions ($F = 194.032$, d.f. = 1, 78, $P = 0.0001$). More



Key:
Baseline = baseline task condition.
Ongoing = Ongoing task condition.
Ongoing (PM1) = RTs to ongoing stimuli only in the PM1 task condition.
PM1 = RTs to prospective memory stimuli only in the PM1 condition.
Ongoing (PM2) = RTs to ongoing stimuli only in the PM2 task condition.
PM2 = RTs to prospective memory stimuli only in the PM2 condition.

Fig. 1. Mean (S.D.) reaction times by condition across tasks.

interestingly, however was the significant slowing of RTs to the non-PM trials in the PM conditions (ongoing $<$ PM1, $F = 35.9$, $P = 0.0001$; ongoing $<$ PM2, $F = 9.5$, $P = 0.007$). There were also practice effects on RT in the comparison between the PM1 condition and PM2 as intended ($F = 8.46$, $P = 0.01$). Within the PM conditions, there was no significant difference in RTs to the prospective memory stimuli compared with the other (ongoing) trials. Fig. 1 shows the RTs in each of the conditions.

Consideration of the errors in each condition showed a comparable pattern. Errors could not be made in the baseline condition. In the ongoing task condition, errors were quite rare (mean per subject = 2.45%, S.D. = 2.33%). This compares to a mean of 5.03% (S.D. = 3.56%) to the equivalent (i.e. non-PM) items in the PM1 condition, and 2.02% (S.D. = 2.1%) in the PM2 condition. This difference is not significant ($F = 1.21$, d.f. = 2, 52, $P = 0.30$). Errors to PM stimuli in the PM1 condition were more common (PM1 mean 8.9% errors (S.D. = 12.4%); PM2 = 6.3% (S.D. = 8.85%)).

3.2. Functional imaging results

The significant regional cerebral blood flow (rCBF) increases associated with contrasts between the conditions and across task formats (i.e. pictures, numbers letters) are shown in Table 2. Only results that were significant at better than $P < 0.05$ after correction for entire brain volume are reported for all regions with one exception. A right hemisphere thalamic rCBF change was predicted under PM conditions by the study of Burgess et al. [4], who found a $Z = 5.41$ rCBF change at Talairach and Tournoux [58] co-ordinates (x, y, z) 6, −12, 6. For this comparison the threshold was accordingly set to $Z = 3.96$.

3.3. Basic contrasts

Data was collapsed across tasks. There was increased blood flow in right temporo-occipital ($P = 0.001$, corrected for entire brain volume) and left inferior parietal regions ($P < 0.034$ corrected) in the baseline condition compared with the ongoing task condition. Performance of the ongoing task condition was associated with rCBF increases in a large medial occipital region centred upon the right cuneus ($P < 0.001$ corrected, see Fig. 2) compared with the baseline condition. The addition of a prospective memory demand to the ongoing task led to decreases in a large left superior rostral medial frontal region (−2, 62, 22; BA 10) plus the right middle temporal gyrus ($P = 0.020$; the comparable left temporal region just missed significance after correction: −56, −18, −20; $Z = 4.44$, uncorrected $P < 0.001$). There were also increases in the right dorsomedial thalamus in almost the same position as previously found [4,57] co-ordinates 6, −12, 6; present study: 6, −16, 6). This degree of cross-study concordance is striking. The principal results are rendered onto a standard brain in Fig. 2.

In the comparison of the first set of prospective memory trials with the second (PM1 versus PM2), data was collapsed across tasks. Under these conditions no rCBF changes reached significance after correction for entire brain volume.

Table 2
Significant regional cerebral blood flow increases

Contrast	BA[a]	Structure	Z	x	y	z[b]
Baseline minus ongoing	19/37	R itg/mog	4.94	58	−64	−4
	40	L ipl	4.44	−68	−38	28
	40	R ipl	4.29	62	−42	34
Ongoing minus baseline	17	R cuneus	5.61	10	−72	10
Ongoing minus prospective memory	10	L sfg	5.24	−2	62	22
	21	R mtg	4.99	58	−2	−18
Prospective memory minus ongoing	–	R M-D thalamus	4.50	6	−16	6

[a] Brodmann's area.

[b] x, y, z: Talairach and Tournoux [58] co-ordinates; R: right hemisphere; L: left hemisphere; M-D thalamus: medio-dorsal nucleus of the thalamus; itg: inferior temporal gyrus; mog: middle occipital gyrus; mtg: middle temporal gyrus; ipl: inferior parietal lobule; sfg: superior frontal gyrus.

However a number of areas did show change if a less stringent criterion was applied ($P < 0.001$ uncorrected). These were: the right ventral frontal lobe (BA 11: 22, 58, −14) and left cerebellum ($Z = 4.16$ and 4.64, respectively) for the PM1 > PM2 contrast; and the left cerebellum, right superior and medial parietal lobe (BA 4 and 6) and left superior temporal lobe (BA 22) for the PM2 > PM1 contrast ($Z = 4.53$, 4.02, 3.96 and 3.84, respectively). There was no suggestion of rCBF change in rostral prefrontal regions with these contrasts.

3.4. rCBF changes associated with changes in reaction time and errors

A straightforward test of the hypothesis that the rCBF changes previously found in PM conditions (compared with ongoing task conditions alone) is attributable to increased task difficulty is to examine correlations between blood flow changes in the brain and changes in reaction times and errors across all tasks. If similar regions are found in this analysis to the subtraction analyses above, it would suggest that whilst blood flow changes in the specified region can occur during the operation of, say, prospective memory, these changes could not be said to be characteristic of performance of this sort of task, and are therefore less interesting from a theoretical standpoint.

The most critical correlations for this hypothesis are probably the rCBF increases associated with increases in reaction time (RT) regardless of task (i.e. across data for all conditions, and all tasks). We found significant rCBF increases associated with increased RT in a number of cortical, subcortical and other regions. The largest significant increase was found in an extra-cerebral region at the base of the brain which is rich in arterial supply structures (centre of cluster [58] co-ordinates 0, −8, −14, $Z = 5.88$). We assume this reflects general brain blood supply increases, and is thus of little theoretical interest. More interestingly, three subcortical structures showed significant (after correction for entire blood flow) rCBF increases: left ventrolateral thalamus (−14, −6, 16, $Z = 5.14$), right putamen (20, 12, 4, $Z = 5.03$) and left cerebellum (−32, −92, −28, $Z = 4.89$). Four cortical structures also showed significant positive correlations: right insula (40, −12, −6, $Z = 4.89$), right middle occipital gyrus (BA 19: 48, −72, 8, $Z = 4.31$), and both the anterior and posterior cingulates (BA 24 and 31: 10, 32, −4, $Z = 4.36$; 18, −64, 24, $Z = 4.87$, respectively).

A large number of cerebral regions also showed significant negative correlations between rCBF and RT (in other words, that rCBF increased as RT decreased). The most highly significant cortical regions were in the temporal and parietal lobes for each hemisphere (for left hemisphere: inferior temporal lobe (BA 37) and superior parietal lobe (BA 37, 7 and 1); right hemisphere: inferior temporal lobe (BA 20), plus occipital pole (BA 17)). We also found again a significant result for the anterior cingulate on the right (BA 24/32, co-ordinates 2, 36, 18, $Z = 4.85$).

Correlations of rCBF with errors showed a rather different pattern. No brain regions showed a significant positive correlation (i.e. rCBF increase as errors increase). And only one significant negative correlation was discovered. This was in the left superior parietal lobe (BA 7: −16, −14, 62, $Z = 4.70$). Overall, the correlation analyses show only two points of overlap with the subtraction analyses even if a very loose criterion for determining overlap is used. These involve the right BA 19/37 region and the thalamus. Critically for the current study, there was no suggestion of correlations between rCBF in the region of BA 10 and changes in either RT or errors.

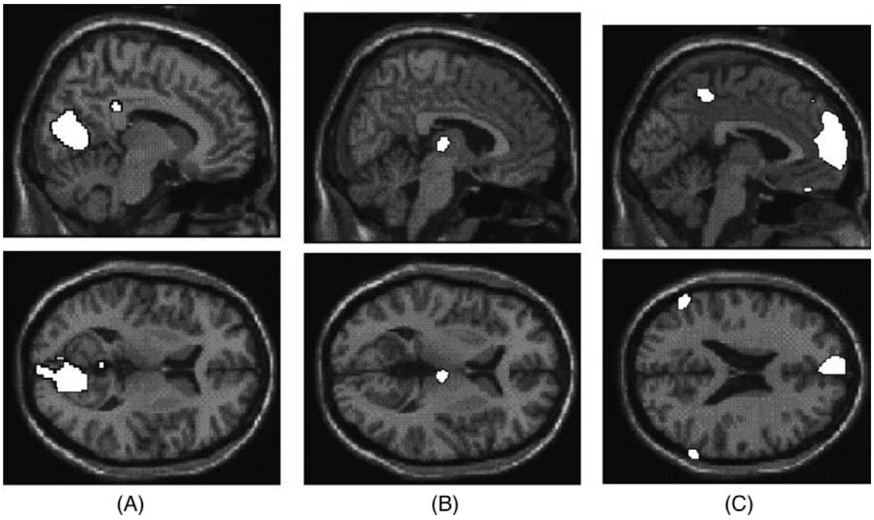


Fig. 2. Representation of selected significant rCBF changes. Column A shows occipital region where blood flow increase occurred in the ongoing relative to the baseline task. Column B shows thalamic rCBF increase in the prospective memory conditions relative to the ongoing task condition. Column C shows the BA 10 decrease in the prospective memory conditions relative to the ongoing task condition.

A further, and especially stringent test of the hypothesis that the rCBF changes reported in Table 2 were associated with changes in task difficulty rather than the specific nature of the demands involved is to repeat the subtraction analyses above whilst entering subjects' mean reaction times and errors across tasks as covariates of no interest.

The results shown in Table 2 were essentially replicated in these covariance analyses. However there were two exceptions. First in the baseline minus ongoing task comparison the right BA 40 focus became non-significant after correction ($Z = 3.42$). Second, the dorsomedial thalamic rCBF change reported in the ongoing task minus prospective memory conditions was removed by the analysis of covariance.

Interestingly, these covariance analyses generally resulted in higher values in pre-existing areas. Thus a number of regions which previously just failed to reach significance after correction now did so. These were: baseline minus ongoing: right BA20/21 inferior parietal lobe; PM minus ongoing: BA 44 inferior frontal gyrus, $Z = 4.77$; ongoing minus PM conditions left lateral temporal lobe (BA21); PM2, PM1 BA 22 superior temporal gyrus, $Z = 3.82$. The critical result for the current study however concerns the ongoing minus PM contrast. The BA 10 activation, although attenuated, remained significant after covariance for both RT and

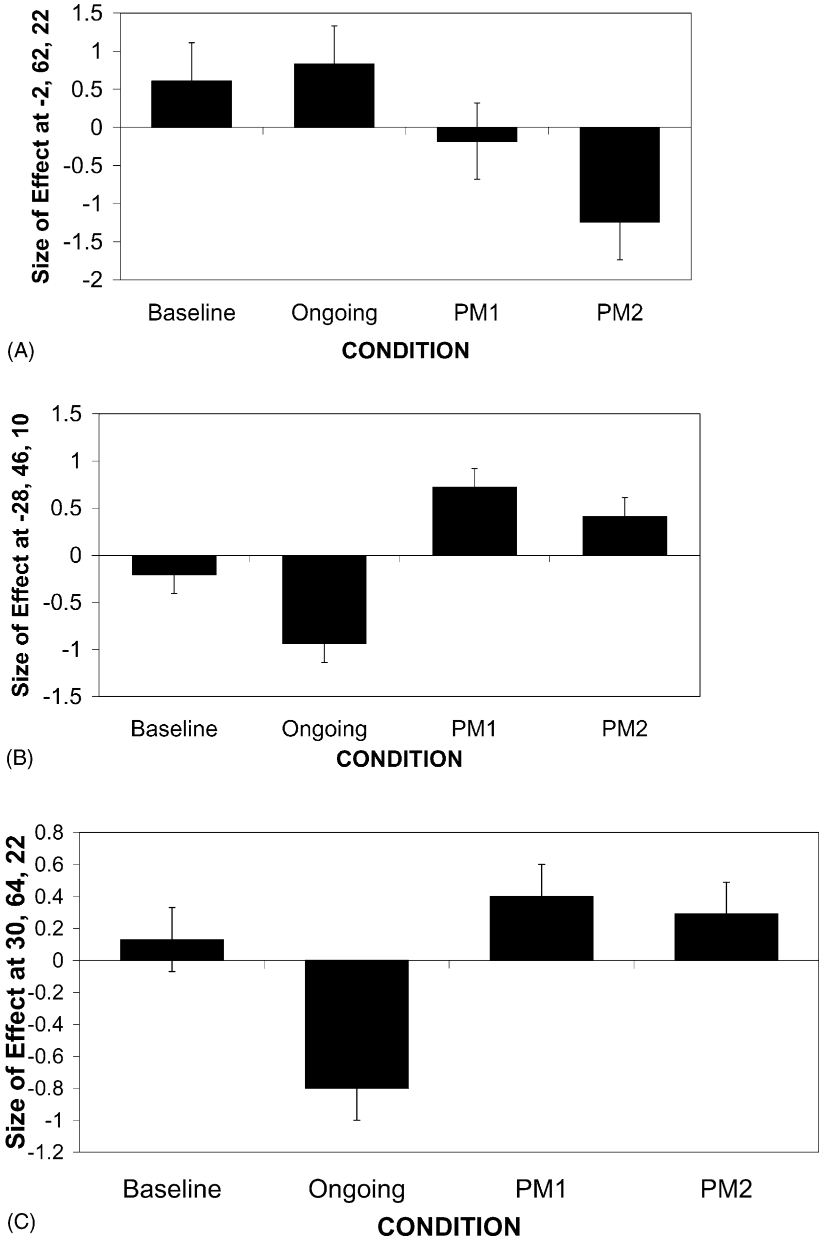
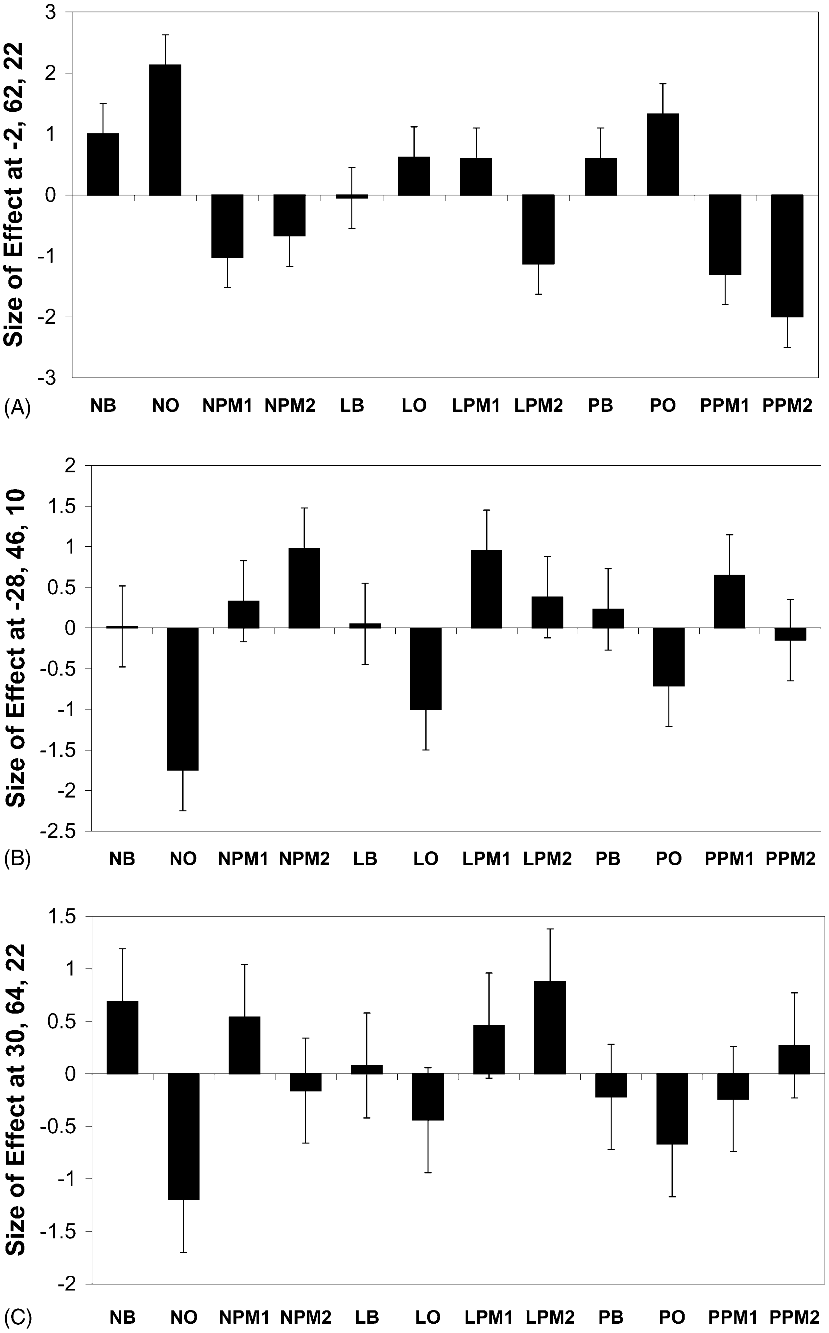


Fig. 3. Relative blood flow changes in rostromedial prefrontal cortex (A) and rostrolateral regions (B) and (C) by condition (data collapsed across three tasks).



Key :

NB = Numbers - Baseline
NO = Numbers - Ongoing
NPM1 = Numbers - Prospective Memory (Novel)
NPM2 = Numbers - Prospective Memory (Practiced)
LB = Letters - Baseline
LO = Letters - Ongoing
LPM1 = Letters - Prospective Memory (Novel)
LPM2 = Letters - Prospective Memory (Practiced)
PB = Pictures - Baseline
PO = Pictures - Ongoing
PPM1 = Pictures - Prospective Memory (Novel)
PPM2 = Pictures - Prospective Memory (Practiced)

Fig. 4. Relative blood flow changes in rostromedial prefrontal cortex (A) and rostrolateral regions (B) and (C) by condition and task.

errors (co-ordinates 0, 62, 22, $Z = 3.80$, $P = 0.039$ after correction). After covariance two previously non-significant regions also became so (left lateral temporal region (BA 21) and right medial temporal lobe (BA 36)). However probably the most significant change in this comparison from a theoretical standpoint came in the ventromedial prefrontal cortex (BA 11). In the basic contrast (i.e. before covariates were entered), this region failed to reach significance after correction (co-ordinates −6, 36, −22, $Z = 3.57$). However after covarying for RT and errors, it became significant (−4, 32, −22, $Z = 4.34$, $P = 0.002$).

3.5. Rostral prefrontal changes across conditions

Whilst the contrasts between the prospective memory and the ongoing task conditions showed polar and rostral prefrontal (BA 10) changes as expected, the result was unexpected in two regards. First the region identified in this study, whilst indeed BA 10, is considerably more medial than the lateral BA 10 regions previously identified as involved in prospective memory (this study: −2, 62, 22; previous study [4]: −30, 62, −6 and 40, 50, 0). Secondly, our previous study showed lateral BA 10 increases in prospective memory conditions relative to the ongoing task alone. However in this study, we found medial BA 10 decreases in the PM conditions.

To investigate the matter of more lateral rostral prefrontal involvement, we performed a series of regions of interest (ROI) analyses upon both the medial rostral region identified here (henceforth called rostromedial), and the lateral regions previously identified (rostrolateral). We interrogated the brain regions lying within a 30 mm sphere of the rostrolateral areas identified in our previous study [4], and identified any subregions within this area that showed significant rCBF change. Collapsing across PM conditions and contrasting with the ongoing task, we found significant increases in the PM conditions in a left rostrolateral area (BA 10; middle frontal gyrus −28, 46, 10; $P = 0.009$ corrected for false discovery rate) and three subregions of lateral BA 10 within the right frontal lobe (foci: 30, 64, 22, $Z = 2.83$; 30, 66, 18, $Z = 2.82$; 36, 52, 18, $Z = 2.39$; all $P = 0.01$ corrected). The relative rCBF changes in these regions occurring in each condition and collapsed across tasks, are shown in Fig. 3A–C (in view of previous findings in this analysis of ventral frontal involvement (BA 11) it should also be noted that this analysis demonstrated a significant right ventrolateral (48, 56, −12; $Z = 2.77$, $P = 0.01$) increase in the PM conditions relative to the ongoing ones. Further analysis showed that this region demonstrated greatest rCBF in the PM1 condition relative to the PM2 and ongoing tasks, which did not differ from each other).

It is immediately apparent from Fig. 3A–C is that the pattern of rCBF change in the rostromedial region is almost the converse of those in the rostrolateral regions. The rostromedial region shows higher blood flow in the baseline and ongoing tasks compared with the prospective memory tasks, and the rostrolateral regions show higher blood flow in the prospective memory conditions relative to the baseline and ongoing conditions.

Furthermore, the pattern generally holds for the three tasks individually. This data is shown in Fig. 4A–C. The most critical comparison for this study is between the ongoing and prospective memory conditions. For the rostromedial region, there is no instance where rCBF in an ongoing condition is lower than in a corresponding PM condition. For the rostrolateral regions, there is no instance of lower rCBF in a PM condition compared with a corresponding ongoing one.

Thus the patterns outlined in Fig. 3A–C are found at the individual task level, and appear to be broadly characteristic of this class of tasks regardless of the precise nature of the stimuli or the to-be-remembered intention.

4. Discussion

4.1. The task difficulty hypothesis

The principal motivation for this experiment was to investigate whether the anterior prefrontal (especially BA 10) rCBF changes implicated in PM paradigms were consistent with either simple task difficulty increases or the increased attention that needs to be paid to the stimuli in order to recognise them as significant. There is no supporting evidence in this study. First consider the data presented in Fig. 3A–C. If we assume that rCBF increases in a neuronal population index the processing operation of that region, then the only pattern in prospective memory tasks of the type used here that would be consistent with a difficulty hypothesis would be one where the baseline task shows relatively smaller rCBF than the ongoing task, which in turn shows smaller rCBF than in the PM conditions. However this pattern is violated for both the medial and lateral BA 10 regions identified here. The medial region show *decreases* in rCBF in the PM conditions relative to the ongoing ones, and the lateral regions show *decreases* in the ongoing condition relative to the much simpler baseline task.

Two other reasons to reject the task difficulty hypothesis were the lack of change to the medial BA 10 result with covariance for changes in RTs and errors, and the lack of correlation between any BA 10 area and RTs and errors, despite a number of other brain regions showing such a relationship. Overall, there is no support in these results for the contention that the BA 10 rCBF changes found both here and in previous functional imaging studies of prospective memory might be attributable to alterations in task difficulty rather than some more specific processing requirement made by situations involving delayed intentions.

As an aside, it might be worth noting that at various stages in the analyses we found significant effects in the ventral frontal region (BA 11): these were a significant rCBF decrease in PM conditions relative to ongoing ones after covarying for RTs and errors in the left posterior ventromedial region; greater rCBF in the unpracticed prospective memory condition (PM1) relative to the practiced conditions (PM2) or ongoing tasks in a right ventrolateral region; and increases in the PM1 conditions over ongoing and PM2 conditions in the most lateral aspects of BA 11 on the right. Generally these effects were not strong. However the recurrent appearance of this region in the analysis does perhaps suggest some role for this region in prospective memory. We do not hold a strong view at this time of what this role might be. However given that so many neurological patients who show prospective memory-type failures in everyday life have suffered damage to this region [3,34], these results may later hold significance for an understanding of their problems.

Of course we do not exclude the possibility that some anterior polar and superior prefrontal regions may be sensitive to task difficulty and/or learning (see e.g. [27,55]). Indeed, the results for the PM1 versus PM2 condition contrasts hint that they may be. However it is clear that this effect in the regions considered here is smaller than that caused by the change in task demands. So, given that the results presented here are inconsistent with a task difficulty hypothesis, what broader interpretation might be given to them?

4.2. Extra-frontal rCBF changes

As regards the rCBF changes outside the frontal lobes are concerned, the regions implicated in the comparisons are generally those about which a relatively large body of data exists. BA 19 and 37 are both part of the occipitotemporal visual pathway [29,60] and have often been implicated in motion perception (e.g. [2,13]); blood flow changes in BA 40 are often seen in attention-demanding tasks (e.g. [9,16,28,35,44,57,61], see [7] for review); changes in the cuneus are often implicated in functional imaging studies where visually presented stimuli are complex or unfamiliar and the operations that need to be performed are effortful [47,59], see [23,54] and retrieval from memory is required [8,25,26,41,62]. BA 21 (lateral mid-temporal lobe) is part of the associative auditory cortex and may be involved in semantic/category discrimination tasks (e.g. [17,40,45]). Overall, these activations are therefore unremarkable, and similar to others discovered using paradigms with obvious similarities.

A more interesting finding concerned the medio-dorsal thalamus. These rCBF changes were straightforwardly in agreement with our previous findings. Burgess et al. [4] found rCBF increases in the thalamus only in the condition where PM stimuli were seen and responded to, rather than just expected. Thus one might expect involvement of the thalamus to be associated either with recognition of the stimuli, recalling the intention, or effecting the intended action. In the present study there was a rCBF increase in the right medio-dorsal thalamus in an equivalent condition, and as noted above, the co-ordinates of the foci of activation in both studies is remarkably similar. The involvement of the medio-dorsal thalamus in other tasks that are not conventional memory-type paradigms (e.g. [51]) and do not have a delayed intention component favours at present the latter interpretation, possibly linked to inhibition of current response modes or selection of possible responses. Whatever the precise role these results signify, it is likely that they are not specific to PM situations, but are nevertheless vital to them, as suggested by human lesion findings [12]. This interpretation is supported by the analysis of covariance, where thalamic involvement was removed by covarying for changes in RT and errors.

4.3. Rostral prefrontal rCBF changes

The most theoretically significant results of this study however concern the rostral prefrontal rCBF changes. That prospective memory might in part involve cognitive control processes supported by frontal lobe structures is a widely held possibility [1,5,22,36,38,53,63]. However it may now be possible to be more specific about the frontal lobe regions involved and the role they play. A consistent finding concerns a large rostral region whose ventral aspect approximates the frontal pole, and extends approximately 30–40 mm superiorly. The largest part of this region is Brodmann's area 10. This region has been implicated in both previous PET studies of prospective memory [4,43] as well as both group and single-case human lesion studies [4,6]. Moreover, central frontal and frontopolar regions have also been implicated in ERP studies of prospective memory [63]. Thus evidence from different methods within cognitive neuroscience is showing promising agreement for a role for the anterior superior and polar aspects of the frontal lobes in prospective memory.

The direction of the results here was however unexpected. In Burgess et al. [4] rCBF increases (relative to ongoing task performance) were found in BA 10 (bilaterally) when participants were expecting to see a PM stimulus even though it never occurred ("expectation condition"). These increased further (although not significantly so) in a condition where they were expecting PM stimuli, they did occur, and were acted upon ("execution condition"). In agreement, Okuda et al. [43] also showed frontopolar rCBF increases in a condition where PM stimuli were expected, encountered, and acted upon. In the present study, however, there were significant BA 10 *decreases* (relative to the ongoing task alone) in the condition where PM stimuli were expected, encountered and acted upon: i.e. a very similar condition to Burgess et al.'s [4] execution condition.

However, whilst the regions involved in both this and the previous study are nominally BA 10, it was clear that the regions under consideration are actually not the same, being more medial and superior in this study (first study: right hemisphere [58] co-ordinates 40, 50, 0 and 44, 56, 4; left hemisphere −30, 62, −6 and −30, 68, 2; present study −2, 62, 22). In summary, the first study showed lateral BA 10 rCBF changes in both hemispheres, and this study showed changes in superior medial BA 10 unilaterally (on the left).

This apparent discrepancy was investigated by examining the rCBF changes across conditions in the rostromedial region identified here, and the rostrolateral regions previously identified [4]. We found that the rostromedial and rostrolateral areas showed remarkably different (indeed, almost opposite) patterns of rCBF change across conditions. The greatest difference in the medial region occurred between the ongoing and practiced (PM2) conditions, with blood flow lower in the latter. The greatest difference in the rostrolateral regions occurred between the ongoing and unpracticed prospective memory conditions (PM1), with blood flow highest in the latter. What then are the important factors in determining the involvement of these different rostral areas?

We will start by excluding factors that must be of little significance. Since the pattern of results was replicated across three different tasks, we can exclude as factors the precise nature of the stimuli (accepting of course the constraint that all stimuli here were presented visually), and the exact nature of the to-be-remembered intention (whilst accepting the limitation that all intentions here were event-based rather than time-based). Since all responses were made in a very similar way it also seems unlikely that the small differences in response method between conditions is a significant factor. We also know that rostrolateral rCBF increases can be seen where targets are merely anticipated rather than actually detected [4], so it is unlikely that these changes reflect processes related to the appearance of targets (e.g. recognition, post-retrieval processing and so forth). And given that we accept that lower rCBF indexes decreased information processing, any factor to do with intention cue or target processing also cannot be relevant to the rostromedial findings, since rCBF was lower in the PM than ongoing conditions.

So if the BA 10 findings do not relate to stimuli, response, appearance or (post-presentation) recognition of cues, or nature of the intention, or the difficulty of the task, what role do they play in prospective memory that might also explain the differences in findings between the two studies?

A clue is perhaps given by previous demonstrations that BA 10 activity can be sensitive to target densities [48,49]. If BA 10 is sensitive to target densities but not to the actual appearance of targets, then it is likely to be an effect that target density has upon stimulus-independent thought (as previously defined). One candidate might be target anticipation. However whilst this might be an explanation for the lateral BA 10 findings it cannot be so for the medial findings, since rCBF was lower in these conditions. A more unifying explanation would rest upon the consequence of maintaining an intention whilst performing an ongoing task. This necessarily requires some attentional withdrawal from the external (i.e. ongoing) stimuli, and a corresponding increase of attentional focus upon internally-generated cognitions. On this account rostromedial areas play a role in maintaining attention upon external stimuli and rostrolateral areas in maintaining attention upon internal cognitions (see [11,31,46] for related accounts). A more complicated possibility is that rostral regions are involved in the voluntary *switching* of attention from an internal cognitive representation (i.e. thinking about something one has in mind) to an external one (i.e. thinking about an external stimulus) rather than the maintenance of attention in either direction. This receives some support from the behavioural results here, where significant slowing occurred on the non-PM trials of the PM conditions: attentional switching of the type described here would be expected to have some RT costs. Moreover this explanation would predict an influence of differing target densities and of practice, since these would alter the requirement for switching attentional focus. On these accounts the slight variation in results between our first study [4] and the present would be a consequence of changes in introspection prompted by the differences in factors such as target density and retention interval. This hypothesis has the additional benefit that models of how it might operate could be quite simple, bear a strong relation to explanations at a haemodynamic level, and could predict the contiguous but converse patterns of activation demonstrated here. There are however other more complex possibilities which cannot be discounted. For instance that the critical processes supported by rostral regions are involved in the *comparison* between internal representations of targets, or transformations of information from external stimuli into a form where comparison with internal targets is possible. Overall however, studies which speak to a characterisation of the functions of this fascinating area of the brain are only just starting to appear, and it is probably too early to take a firm view at present.

There are two final matters worthy of discussion. The first concerns the degree to which the paradigms used in this study conform to characteristic 5 given in Table 1: that in a prospective memory situation, performance of the ongoing task should prevent continuous, conscious rehearsal of the intention over the entire delay period. This matter has caused considerable debate amongst prospective memory theorists. Some believe that any internal rumination upon the intended action should be considered an intention retrieval event. According to this view, any slowing to *non-PM* trials in a PM paradigm as occurred here is likely evidence of rumination, and therefore that the actual “retention interval” is likely to be smaller in duration than the period between intention creation and an actual response to an intention cue. Some theorists wish to disregard as relevant to the study of delayed intentions results from paradigms where this period does not reach a given duration. Indeed at academic conferences we have actually heard various time limits being proposed, which have varied from as little as a few seconds to many hours or even days. We maintain however that this is an unnecessarily narrow view both of the everyday experience of delayed intentions, and of the phenomena which should be relevant to the field of prospective memory. We take no view of the duration of the retention interval that is required before a paradigm can be classified as a “prospective memory” paradigm. We only require that conscious and wholly continuous rehearsal (of the intention) of the type necessary for the performance of, say, a typical short-term memory task (e.g. digit span) is not possible. This may be evidenced by the production of a response to a (quite difficult) question which is irrelevant to the intention. Typically in an experimental situation this is a response to those stimuli which are not intention cues. This is justified by our view that in most everyday situations involving a delayed intention there is some rumination (i.e. rehearsal) of the intention before the retrieval context occurs and it would be theoretically precarious and probably practically impossible to set an arbitrary limit on this duration before classifying a paradigm as a “prospective memory” one. Furthermore it is our opinion that it would be unfortunate to view as not relevant to the study of delayed intentions the processes, behaviours and situational factors involved in this rumination; the effect that it has on eventual task success; and indeed the subjective experience of the subject at these times.

The second matter for discussion is the degree to which the present results can be taken as evidence of a “dissociation” in functions between medial and lateral rostral prefrontal regions. It is doubtful that functional imaging data can ever provide data of equivalent theoretical power in this regard to a classic double dissociation in human lesion studies. There are many reasons for this, e.g. the possibility of group averaging artefact; difficulties in establishing an independently-derived or universal “baseline” or scale; the difficulty of excluding confounds (e.g. unforeseen influence of non-critical task components; complex mediating variables) and so forth. However given these caveats, and the limitations of the PET method and our primitive experimental procedures, the data here are probably as strong an indicator of double dissociation between the regions as might be expected: we found that when a delayed intention component was added to a task, blood flow in rostromedial prefrontal cortex showed significant decrease, and blood flow in rostrolateral prefrontal areas showed significant increase. Thus the results lend strong support for a double dissociation between medial and lateral rostral regions in prospective memory situations (see also [32]).

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References

[1] Bisiacchi PS. The neuropsychological approach in the study of prospective memory. In: Brandimonte M, Einstein GO, McDaniel MA, editors. Prospective memory: theory and applications. Mahwah, NJ: Lawrence Erlbaum; 1996. p. 297–317.

[2] Brandt T, Stephan T, Bense S, Yousry TA, Dieterich M. Hemifield visual motion stimulation: an example of interhemispheric cross-talk. Neuroreport 2000;11:2803–9.

[3] Burgess PW. Strategy application disorder: the role of the frontal lobes in human multitasking. Psychological Research 2000;63:279–88.

[4] Burgess PW, Quayle A, Frith CD. Brain regions involved in prospective memory as determined by positron emission tomography. Neuropsychologia 2001;39:545–55.

[5] Burgess PW, Shallice T. The relationship between prospective and retrospective memory: neuropsychological evidence. In: Conway, MA, editor. Cognitive models of memory. Hove, UK: Psychology Press; 1997. p. 247–72.

[6] Burgess PW, Veitch E, De Lacy Costello A, Shallice T. The cognitive and neuroanatomical correlates of multitasking. Neuropsychologia 2000;38:848–63.

[7] Cabeza R, Mangels J, Nyberg L, Habib R, Houle S, McIntosh AR, et al. Brain regions differentially involved in remembering what and when: a PET study. Neuron 1997;19:863–70.

[8] Cabeza R, Nyberg L. Imaging cognition: an empirical review of PET studies with normal subjects. Journal of Cognitive Neuroscience 1997;9:1–26.

[9] Coull JT, Frith CD, Frackowiak RSJ, Grasby PM. A fronto-parietal network for rapid visual information processing: a PET study of sustained attention and working memory. Neuropsychologia 1996;34:1085–95.

[10] Craik FIM, Kerr SA. Prospective memory, aging and lapses of attention. In: Brandimonte M, Einstein GO, McDaniel MA, editors. Prospective memory: theory and applications. Mahwah, NJ: Lawrence Erlbaum; 1996. p. 227–47.

[11] Christoff K, Gabrieli JDE. The frontopolar cortex and human cognition: evidence for a rostrocaudal hierarchical organisation within the human prefrontal cortex. Psychobiology 2000;28:168–86.

[12] Daum I, Ackermann H. Frontal-type memory impairment associated with thalamic damage. International Journal of Neuroscience 1994;77:187–98.

[13] Dupont P, Orban GA, De Bruyn B, Verbruggen A, Mortelmans L. Many areas in the human brain respond to visual motion. Journal of Neurophysiology 1994;72:1420–4.

[14] Einstein GO, McDaniel MA. Normal aging and prospective memory. Journal of Experimental Psychology 1990;16:717–26.

[15] Ellis J, Kvavilashvili L, Milne A. Experimental tests of prospective remembering: the influence of cue-event frequency on performance. British Journal of Psychology 1999;90:9–23.

[16] Fink GR, Halligan PW, Marshall JC, Frith CD, Frackowiak RSJ, Dolan RJ. Neural mechanisms involved in the processing of global and local aspects of hierarchically organized visual stimuli. Brain 1997;120:1779–91.

[17] Friederici AD, Optiz B, Von Cramon DY. Segregating semantic and syntactic aspects of processing in the human brain: a fMRI investigation of different word types. Cerebral Cortex 2000;10:698–705.

[18] Friston KJ, Ashburner J, Poline J-B, Frith CD, Heather JD, Frackowiack RSJ. Spatial registration and normalisation of images. Human Brain Mapping 1995a;2:165–89.

[19] Friston KJ, Frith CD, Liddle PF, Dolan RJ, Lammertsma AA, Frackowiak RSJ. The relationship between global and local changes in PET scans. Journal of Cerebral Blood Flow and Metabolism 1990;10:458–66.

[20] Friston KJ, Holmes AP, Worsley KJ, Poline J-B, Frith CD, Frackowiak RSJ. Statistical parametric mapping in functional imaging: a general linear approach. Human Brain Mapping 1995b;2:-189–210.

[21] Friston KJ, Price CJ, Fletcher O, Moore C, Frackowiack RSJ, Dolan RJ. The trouble with cognitive subtraction. Neuroimage 1996;4:97–104.

[22] Glisky EL. Prospective memory and the frontal lobes. In: Brandimonte M, Einstein GO, McDaniel MA, editors. Prospective memory: theory and applications. Mahwah, NJ: Lawrence Erlbaum; 1996. p. 249–66.

[23] Goldberg TE, Berman KF, Fleming K, Ostrem J, Van Horn JD, Esposito G, et al. Uncoupling cognitive workload and prefrontal cortical physiology: a PET rCBF study. Neuroimage 1998;7:296–303.

[24] Graf P, Uttl B. Prospective memory: a new focus for research. Consciousness and Cognition 2001;10(4):437–50.

[25] Grasby PM, Frith CD, Friston KJ, Simpson J, Fletcher PC, Dolan RJ, et al. A graded task approach to the functional mapping of brain areas implicated in auditory-verbal memory. Brain 1994;117:1271–82.

[26] Iidaka T, Anderson ND, Kapur S, Cabeza R, Craik FIM. The effect of divided attention on encoding and retrieval in episodic memory revealed by positron emission tomography. Journal of Cognitive Neuroscience 2000;12:267–80.

[27] Jansma JM, Ramsey NF, Slagter HA, Kahn RS. Functional anatomical correlates of controlled and automatic processing. Journal of Cognitive Neuroscience 2001;13:730–43.

[28] Johannsen P, Jakobsen J, Bruhn P, Hansen SB, Gee A, Stodkilde-Jorgensen H, et al. Cortical sites of sustained and divided attention in normal elderly humans. Neuroimage 1997;6:145–55.

[29] Kassubek J, Otte M. Brain imaging in a patient with hemimicropsia. Neuropsychogia 1999;37(12):1327–34.

[30] Kliegel M, McDaniel M, Einstein GO. Plan formation, retention, and execution in prospective memory: a new approach and age-related effects. Memory and Cognition 2000;28:1041–9.

[31] Koechlin E, Basso G, Pietrini P, Panzer S, Grafman J. The role of the anterior prefrontal cortex in human cognition. Nature 1999;399(6732):148–51.

[32] Koechlin E, Corrado G, Pietruni P, Grafman J. Dissociating the role of the medial and lateral anterior prefrontal cortex in human planning. Proceedings of the National Academy of Sciences of the United States of America 2000;97:7651–6.

[33] Kvavilashvili L. Remembering intentions: testing a new method of investigation. Applied Cognitive Psychology 1998;12:533–54.

[34] Levine B, Stuss DT, Milberg WP, Alexander MP, Schwartz M, Macdonald R. The effects of focal and diffuse brain damage on strategy application: evidence from focal lesions, traumatic brain injury, and normal ageing. Journal of the International Neuropsychological Society 1998;4:247–64.

[35] Lewin JS, Friedman L, Wu D, Miller DA, Thompson LA, Klein SK, et al. Cortical localisation of human sustained attention: detection with functional MR using a visual vigilance paradigm. Journal of Computer Assisted Tomography 1996;20:695–701.

[36] Marsh RL, Hicks JL. Event-based prospective memory and executive control of working memory. Journal of Experimental Psychology: Learning, Memory, and Cognition 1998;24:336–49.

[37] Marsh RL, Hicks JL, Landau JD. An investigation of everyday prospective memory. Memory and Cognition 1998;26:633–43.

[38] McDaniel MA, Glisky EL, Guynn MJ, Routhieaux BC. Prospective memory: a neuropsychological study. Neuropsychology 1999;13:103–10.

[39] McGuire PK, Paulesu E, Frackowiak RS, Frith CD. Brain activity during stimulus independent thought. Neuroreport 1996;7:2095–9.

[40] Mirz F, Ovesen T, Ishizu K, Johannsen P, Madsen S, Gjedde A, et al. Stimulus-dependent central processing of auditory stimuli: a PET study. Scandanavian Audiology 1999;28:161–9.

[41] O'Driscoll GA, Wolff AL, Benkelfat C, Florencio PS, Lal S, Evans AC. Functional neuroanatomy of smooth pursuit and predictive saccades. Neuroreport 2000;11:1335–40.

[42] Okuda J, Fujii T, Ohtake H, Tsukiura T, Suzuki K, Kawashima R, et al. Prefronto-hippocampal systems underlying voluntary and reflexive control of prospective remembering, submitted for publication.

[43] Okuda J, Fujii T, Yamadori A, Kawashima R, Tsukiura T, Fukatsu R, et al. Participation of the prefrontal cortex in prospective memory: evidence from a PET study in humans. Neuroscience Letters 1998;253:127–30.

[44] Pardo JV, Fox PT, Raichle ME. Localisation of a human system for sustained attention by positron emission tomography. Nature 1991;349:61–4.

[45] Perani D, Schnur T, Tettamanti M, Gorno-Tempini M, Cappa SF, Fazio F. Word and picture matching: a PET study of semantic category effects. Neuropsychologia 1999;37:293–306.

[46] Pollman S. Switching between dimensions, locations and responses: The role of the left frontpolar cortex. Neuroimage 2001;14:118–24.

[47] Reber PJ, Stark CE, Squire LR. Cortical areas supporting category learning identified using functional MRI. Proceedings of the National Academy of Science of the United States of America 1998;95:747–50.

[48] Rugg MD, Fletcher PC, Chua PM, Dolan RJ. The role of the prefrontal cortex in recognition memory and memory for source: a fMRI study. Neuroimage 1999;10:520–9.

[49] Rugg MD, Fletcher PC, Frith CD, Frackowiak RSJ, Dolan RJ. Differential activation of the prefrontal cortex in successful and unsuccessful memory retrieval. Brain 1996;119:2073–83.

[50] Schaefer EG, Kozak MV, Sagness K. The role of enactment in prospective memory. Memory and Cognition 1998;26:644–50.

[51] Scott SK, Holmes A, Friston KJ, Wise RJS. A thalamo-prefrontal system for representation in executive response choice. Neuroreport 2000;11:1523–7.

[52] Shallice T. The neuropsychology of prospective memory. In: Brandimonte M, Einstein GO, McDaniel MA, editors. Prospective memory: theory and applications. Mahwah, NJ: Lawrence Erlbaum; 1996. p. 319–25.

[53] Shapiro JK, Shapiro LR, Russell S, Alper JS. A role for executive processes in prospective remembering. Brain and Cognition 1998;37:175–7.

[54] Shulman GL, Corbetta M, Buckner RL, Raichle ME, Fiez JA, Miezin FM, et al. Top–down modulation of early sensory cortex. Cerebral Cortex 1997;7(3):193–206.

[55] Siegel BV, Nuechterlein KH, Abel L, Wu JC. Glucose metabolic correlates of continuous performance test performance in adults with a history of infantile autism. Schizophrenia Resolutions 1995;17(1):85–94.

[56] Strange BA, Henson RNA, Friston KJ, Dolan RJ. Anterior prefrontal cortex mediates rule learning in humans. Cerebral Cortex 2001;11:1040–6.

[57] Sturm W, de Simone A, Krause BJ, Specht K, Hesselmann V, Radermacher I, et al. Functional anatomy of intrinsic alertness: evidence for a fronto–parietal–thalamic–brainstem network in the right hemisphere. Neuropsychologia 1999;37:797–805.

[58] Talairach J, Tournoux P. Co-planar stereotactic atlas of the human brain. Stuttgart: Thieme (Georg); 1988.

[59] Tan LH, Feng CM, Fox PT, Gao JH. An fMRI study with written Chinese. Neuroreport 2001;12(1):83–8.

[60] Tan LH, Spinks JA, Gao JH, Liu HL, Perfetti CA, Xiong J, et al. Brain activation in the processing of Chinese characters and words: a functional MRI study. Human Brain Mapping 2000;10:16–27.

[61] Van Horn J, Ellmore TM, Esposito G, Berman KF. Mapping voxel-based statistical power on parametric images. Neuroimage 1998;7:97–107.

[62] Vanni S, Tanskanen T, Seppa M, Uutela K, Hari R. Coinciding early activation of the human primary visual cortex and anteromedial cuneus. Proceedings of the National Academy of Science of the United States of America 2001;98:2776–80.

[63] West R, Herndon RW, Ross-Munroe K. Event-related neural activity associated with prospective remembering, submitted for publication.