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A fronto-parietal network for rapid visual information processing: a PET study of sustained attention and working memory

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Abstract—The rapid visual information processing (RVIP) task, a test of sustained attention which also requires working memory for its successful execution, has been used in a number of human psychopharmacological studies. Single digits are presented in quick succession (100 or 200 digits/min) on a computer screen, and target sequences of numbers must be detected with a button press. Although previous neuroimaging studies have implicated the frontal and parietal cortices in performance of simple sustained attention tasks, the neuroanatomical substrates of RVIP performance are not yet known. This information would prove invaluable in the interpretation of drug effects on this task, possibly delineating a neuronal network for neurotransmitter action. Therefore, this study investigated the functional anatomy of the RVIP task using positron emission tomography (PET) derived measures of regional cerebral blood flow (rCBF) in eight healthy volunteers. Subjects were required to perform variants of the RVIP task which manipulated both the level of working memory load and the speed of stimulus presentation. Compared with a rest condition (eyes closed), the RVIP task increased rCBF bilaterally in the inferior frontal gyri, parietal cortex and fusiform gyrus, and also in the right frontal superior gyrus rostrally. In comparison with a simple sustained attention control condition, the aforementioned right frontal activations were no longer apparent. We suggest that these data are consistent with the existence of a right fronto-parietal network for sustained, and possibly selective, attention, and a left fronto-parietal network for the phonological loop component of working memory. Copyright © 1996 Elsevier Science Ltd.

Key Words: frontal; vigilance; selective attention; phonological loop; inter-stimulus interval; functional imaging.

Introduction

Sustained attention (or vigilance) can be defined as the ability to maintain attention on a series of stimuli over a period of time, in order to detect infrequent targets, and positron emission tomography (PET) studies have localized areas associated with sustained attention in the right prefrontal and superior parietal cortices [10, 39]. While an investigation by Pardo *et al.* [39] used visual and somatosensory vigilance tasks, a study reported by Cohen *et al.* [10] employed an auditory vigilance task. Activation of the prefrontal cortex in all three vigilance tasks suggests that this area mediates sustained attention, regardless of the modality in which the task is presented.

While the tasks used in these studies measured sustained attention in its simplest form (detecting infrequent targets), other vigilance tasks widely used in neuropsychological and psychopharmacological investigations can be rather more complex. Tasks of the 'Bakan' type [5] require subjects to detect a target and then to maintain attention in order to determine whether it is immediately followed by another, related, target (e.g. during the Continuous Performance Test [48], subjects are asked to respond to the letter 'A' only if preceded by the letter 'X'). The Rapid Visual Information Processing task (RVIP) is another task of this type using digits rather than letters and, though primarily a test of visual sustained attention, it also requires both selective attention and working memory for its successful execution. The test was used originally to determine the effects of cholinergic drugs on attentional performance [32, 49, 55], and has been used more recently to show deleterious effects of the mixed $\alpha 1/\alpha 2$ adrenoceptor agonist clonidine in comparison with the benzodiazepine diazepam in healthy volunteers [14], and also putative therapeutic effects of the

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α2 antagonist idazoxan in patients with dementia of frontal type [16]. In all cases, however, it is still uncertain in which region of the brain, or indeed on which cognitive component of the task, the psychoactive agent is exerting its effect. Therefore, the present investigation attempts to elucidate the brain areas involved in performance of the RVIP task by using radiolabelled $H_2{}^{15}O$ in a PET cognitive activation study with healthy volunteers. A semi-factorial cognitive subtraction design was used in order to draw conclusions about the functional nature of some of these brain areas, which may then be used in the interpretation of psychopharmacological studies.

Working memory is one of the cognitive components of the RVIP task because up to two digits must be held 'on-line', in order to reject or accept subsequent digits as part of a target sequence. Thus, areas of neural activation produced by performance of the RVIP task may be due to either the sustained attention or the working memory components of the task. Therefore, we have modified the working memory requirements of the RVIP task such that subjects were required to detect targets which were two or three digits in length. By comparing these two conditions, we sought to delineate specific neural areas associated with increasing working memory load and, therefore, to clarify interpretation of the areas activated by the RVIP task as a whole. In a recent fMRI study, Cohen *et al.* [11] used a task similar to the visual Continuous Performance Test which activated middle and inferior frontal gyri bilaterally. The authors concluded that these areas mediate the working memory processes required for task performance, although the differences between their experimental and control tasks may not represent just working memory, since both tasks differ also in the degree of selective, and perhaps also sustained, attention required. Selective attention may be defined as the selection of specific pre-defined stimuli for further processing. In both Cohen *et al.*'s task and the RVIP task, it is necessary to attend selectively to stimuli which may form the beginning of a target sequence and to disregard those which may not. This selected stimulus may then be transferred into working memory, where it is compared with the subsequent stimulus for rejection or inclusion as a target sequence, as mentioned previously. It should be noted also that the frontal cortex was the only brain area analysed. Other brain areas, such as the parietal cortex or thalamus which have been activated in working memory [43] and selective attention [34] paradigms respectively, were not imaged. Our experiment allows a comparison of the RVIP task with a control task, as in Cohen *et al.*'s study, but in addition it manipulates working memory load explicitly to test the conclusions of Cohen *et al.* [11], and also to delineate the neural areas involved in the working memory component of RVIP performance.

Another important consideration for the RVIP task is the speed of stimulus presentation. A previous study [14] has noted clonidine-induced RVIP impairments, which were constant throughout the entire duration of a 6 min task (the 'level of vigilance' [17]), when the stimuli were presented at a rate of 100 digits/min. However, exactly the same dose of clonidine, in a comparable group of subjects, produced impairments as a function of time on task (the 'vigilance decrement' [17]) when stimuli were presented at a faster rate (200 digits/min) [13]. This is consistent with the findings of Parasuraman [38], who concludes that while the level of vigilance may be related directly to levels of arousal, the vigilance decrement is observed when a subject must expend mental effort in order to cope with an additional memory load (as in the RVIP task) combined with a fast presentation rate. Our investigation employs a second modification to the RVIP task whereby sequences of embedded targets, two or three digits long, were presented at a rate of either 100 ('standard') or 200 ('fast') digits/min. By comparing the relative rCBF profiles under these two speeds, brain areas sensitive to presentation speed can be identified, and so may delineate areas which are activated by increased effort.

Methods

Subjects

Four right-handed and four left-handed male volunteers took part in the study (mean age = 24.38 years; S.E. = 0.38); all were University graduates. Subjects were physically fit, and none was taking medication. The study was approved by the Hammersmith Hospital ethics committee, and permission to administer radioactive substances was obtained from the Advisory Committee on Radioactive Substances (ARSAC) U.K. Written informed consent was obtained prior to the study.

PET scanning

Scans of the distribution of CBF were obtained for each subject in a quiet, darkened room, using a CTI model 953B PET-scanner (CTI Inc., Knoxville, TN, U.S.A.) with collimating septa retracted. Radioactivity was administered as a $H_2{}^{15}O$ bolus, infused over 20 sec, followed by a 20 sec saline flush. The effective dose equivalent of radioactivity per subject was 7.0 mSv. Twelve PET emission scans were collected over 2 hr, with a 10 min interval between scans. Integrated radioactivity counts accumulated over a 90 sec acquisition period, beginning with the rising phase of radioactivity counts in the head, were used as an index of rCBF. A transmission scan was collected prior to the emission scans to correct for the attenuating effects of the tissues of the head. All active experimental conditions began 60 sec before the start of the data acquisition period, and lasted for its duration.

Experimental design

There were six experimental conditions, each duplicated, resulting in 12 PET scans. In order to minimize the confounding of practice effects with task-induced changes in rCBF, presentation of each experimental condition was randomized across the 12 scans for each subject (i.e. within-subject randomization). In addition, the order of presentation was different for each of the eight subjects (i.e. between-subject randomization). A semi-

factorial design was used, such that in addition to one rest condition and one control condition, there were four RVIP conditions varying in terms of both working memory load and speed of stimulus presentation (see Fig. 1).

Cognitive tasks

The tasks used were all variations of the Rapid Visual Information Processing task [14, 49, 55], which is primarily a test of visual sustained attention, but also requires working memory for its successful execution. Digits were presented one at a time, in pseudo-random order, in the centre of an Apple Macintosh computer screen at a rate of either 100 digits/min ('standard' rate) or 200 digits/min ('fast' rate) for 2.5 min. Subjects were required to detect consecutive sequences of two (*viz.* 2–4; 3–5; 4–6; 5–7) or three (*viz.* 1–3–5; 2–4–6; 3–5–7; 4–6–8) digits and to register responses with a mouse-press using their right index finger. The four combinations of the two independent variables (speed of presentation and working memory load) comprised four of the six experimental conditions (two standard; three standard; two fast; three fast). Another condition was a control task, which similarly presented pseudo-random digits on the computer screen at a rate of 100 digits/min for 2.5 min, but required subjects simply to respond to the occurrence of single '0's. In all cases, target sequences occurred at the rate of four every 30 sec, and the computer calculated both the number of mouse-presses to targets within a period of 1.5 sec post-presentation ('hits') and also the number of mouse-presses which incorrectly identified a target ('false alarms'). Calculations derived from Signal Detection Theory [35, 50] were performed also, in order to take both hit probability and false alarms into consideration in a single measure of either detection sensitivity (A′) or response bias (B″) (see Sahgal, [50] for methods of calculation). A rest state also was included in the design, whereby subjects were asked to lie quietly with eyes closed and to think 'vague' thoughts.

Data analysis

Performance data were analysed using a repeated measures ANOVA, with working memory load and speed of presentation as within-subjects factors. Images were analysed using statistical parametric mapping ([23]; software from the Wellcome Dept of Cognitive Neurology, London, U.K.) implemented in MATLAB (Mathworks Inc., Sherborn, MA, U.S.A.) and run on a SPARC workstation (Sun Microsystems Inc., Surrey, U.K.).

Anatomical normalization

Each of the 12 rCBF images were reconstructed into 31 transverse planes using three-dimensional algorithms, which were then interpolated to 43 planes in order to render the voxels approximately cubic. All rCBF images were then automatically realigned to the first, in order to correct for head movement between scans, and were subsequently normalized into a standard stereotactic space [52] to allow for pixel-by-pixel averaging across subjects. Images were then smoothed using a Gaussian filter of $20 \times 20 \times 12$ mm (full width at half-maximum in the x-, y- and z-planes, respectively), to accommodate inter-subject differences in gyral and functional anatomy and to increase the signal-to-noise ratio in the images.

	Working memory load	
	Standard	Standard
Speed	2-digit sequence	3-digit sequence
	Fast	Fast
	2-digit sequence	3-digit sequence

Fig. 1. Stimulus properties in the four experimental RVIP tasks. Each condition varies in terms of both working memory load (target sequences which are 2 or 3 digits in length) and speed of stimulus presentation (standard = 100 digits/min; fast = 200 digits/min).

Co-variance of global rCBF

Analysis of co-variance (ANCOVA) was used to remove the confounding effects of differences in global activity both within and between subjects [22, 57]. For each pixel in stereotactic space, the ANCOVA generated 12 condition-specific adjusted rCBF values (normalized to a global activity of 50 ml/100 ml/min) with an associated adjusted error variance.

Statistical analysis

Areas of significant change in brain activity, as specified by appropriately weighted linear contrasts, were determined using the t-statistic on a pixel by pixel basis. The resulting set of t-values constituted the statistical parametric map (SPM) [23]. A comparison of the rCBF profile produced by the rest state with that produced by the collective RVIP conditions was predicted to define areas of neural activity associated with performance of the RVIP task. Comparisons of all four RVIP conditions with the control condition, however, were predicted to define neural correlates of 'RVIP-specific' cognitive processes, such as verbal working memory and selective attention. That is to say, those processes other than motor responding, primary visual processing and simple visual sustained attention which are involved in performance of the control task. In addition, the areas of brain activity associated with an increase in either (a) working memory load or (b) speed of presentation were determined by a comparison of rCBF profiles produced by (a) the mean of the two-digit vs the three-digit sequence tasks or (b) the mean of the standard vs the fast speed tasks. An additional correlational analysis was performed on all but the rest scans in order to look at the relationship between rCBF change and task performance (measured in terms of A′). Due to the large number of t-tests involved in these analyses, P-values were corrected for multiple comparisons (using a calculation based on the theory of Gaussian fields [24]) in order to reduce the probability of making Type I errors, and only activations which have significant corrected P-values ($P < 0.05$) are reported. Additionally, in order to avoid incorrectly rejecting significant areas of activation (i.e. Type II errors), a less conservative threshold for significance ($P < 0.001$ uncorrected for multiple comparisons) was adopted only for areas which were hypothesized previously to be activated, based on existing literature. Specifically, these areas comprise the prefrontal cortex, parietal cortex and thalamus for the comparison of RVIP tasks to rest and control conditions [10, 33, 39], and the prefrontal and parietal cortex for the comparison of two-digit to three-digit sequences [11, 43].

Results

RVIP performance

Performance of the RVIP test was impaired significantly in terms of the sensitivity index measure (A′)

when either speed of stimulus presentation [$F(1,7)=54.07$, $P<0.0001$] or working memory load was increased [$F(1,7)=7.97$, $P<0.03$] (Fig. 2). However, there were no effects of speed or working memory load on response bias (B″). In addition, there were no significant interactions between speed and working memory load for either A′ or B″.

Increases in rCBF

RVIP–rest. Significant regional increases of rCBF were found bilaterally in the inferior frontal gyri and parietal cortices, and also in the fusiform gyri bilaterally. Activity in the right inferior frontal gyrus extended across the premotor cortex (x-, y- and z-co-ordinates = 44, −6, 40). Additional significant activations were observed in the calcarine sulcus (primary visual cortex V1), supplementary motor area and the right superior frontal gyrus rostrally [see Table 1 and Fig. 3(a)]. Two further activations of note were observed when a less conservative threshold for significance was adopted ($P<0.001$ uncorrected for multiple comparisons). Related rCBF increases were noted in the left thalamus (x-, y- and z-co-ordinates = −10, −14, 4; $Z=3.29$), and also in the midbrain at the level of the red nucleus and superior colliculus (x-, y- and z-co-ordinates = −6, −22, −4; $Z=3.13$).

RVIP–control. This comparison produced significant increases of rCBF bilaterally in the occipital/fusiform

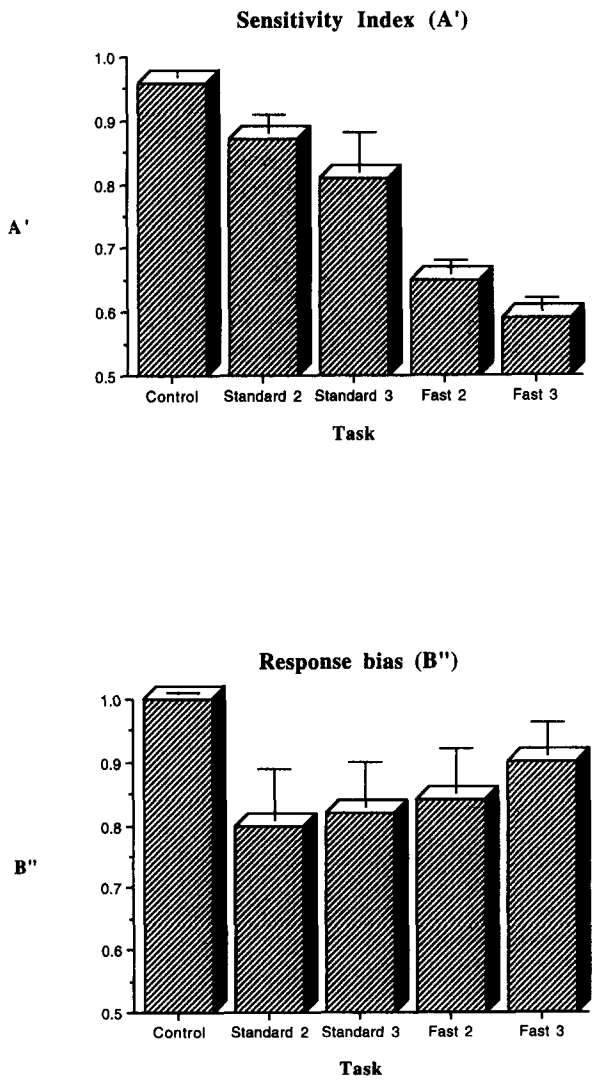

Fig. 2. Accuracy of RVIP performance for each of the experimental manipulations and the control condition, as measured both by signal detection measures of accuracy (A′) and response bias (B″).

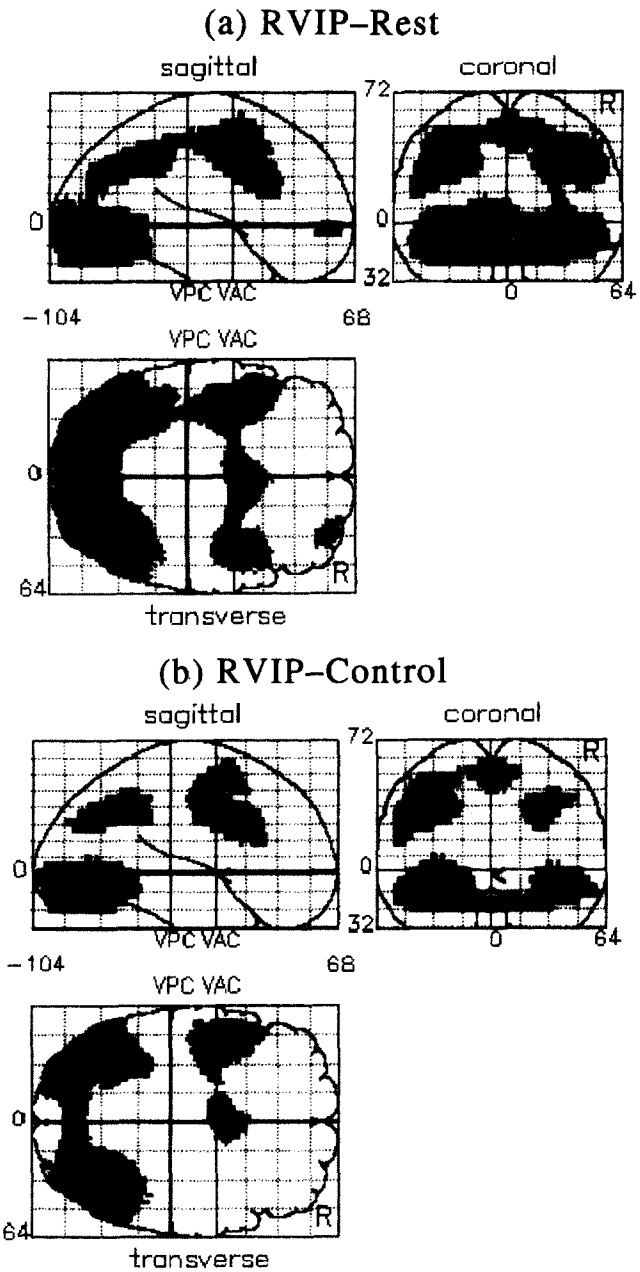

Fig. 3. Statistical parametric maps (SPMs) showing task-induced increases in rCBF when all RVIP tasks are compared to (a) rest (eyes closed) or (b) control task (visual sustained attention). Significant pixels ($Z>4.20$) are displayed in sagittal, coronal and tranverse sections for each comparison (R = right hemisphere).

Table 1. Stereotactic co-ordinates (from [52]) of maximal regional increases of rCBF when all four RVIP tasks were collectively compared with rest*

Anatomical area	*x*, *y*, *z* co-ordinates (mm)	Brodmann's area	*Z*-score
Fusiform gyrus (L)	−20, −90, −16	18	9.63
Fusiform gyrus (R)	32, −90, −12	18	8.93
Primary visual cortex	4, −94, 0	17	4.21
Parietal cortex (L)			
Inferior gyrus	−32, −54, 40	40	6.01
Superior gyrus	−28, −60, 36	7	5.22
Superior parietal gyrus (R)	24, −64, 36	7	6.10
Supplemetary motor area	2, 6, 52	6	5.85
Frontal cortex (L)			
Inferior gyrus	−42, 6, 32	8/44	6.39
Middle/inferior gyrus	−48, 16, 28	9/44	5.96
Frontal cortex (R)			
Inferior gyrus	42, 8, 28	44	4.37
Middle/superior gyrus	34, 52, −4	10	4.78

*The *Z*-score is a measure of significant change, with the threshold for significance being set at $Z > 4.20$ ($P < 0.05$ corrected for multiple comparisons).

and parietal cortex, and in the left inferior frontal gyrus and supplementary motor area [see Table 2 and Fig. 3(b)]. In addition, the right inferior frontal gyrus (*x*-, *y*- and *z*-co-ordinates = 50, 10, 28), corresponding to Brodmann's area 44, was activated, but only when a less conservative threshold for significance was adopted ($Z = 3.46$, $P < 0.001$ uncorrected for multiple comparisons). At the same threshold for significance, rCBF increases ($Z = 3.62$, $P < 0.001$ uncorrected for multiple comparisons) were noted in the left thalamus (*x*-, *y*- and *z*-co-ordinates = −10, −14, 8).

Effect of presentation speed (fast–standard). Significant increases of rCBF were found bilaterally extending across the lateral occipital cortex and fusiform gyrus (*x*-, *y*- and *z*-co-ordinates = −42, −80, −12; $Z = 4.91$ on the left, and 44, −78, −8; $Z = 4.76$ on the right).

Effect of increasing working memory load (three digit–two digit). There were no significant differences in rCBF identified by this comparison.

Decreases in rCBF

Rest–RVIP. Significant decreases of rCBF (Fig. 4) were observed in the medial and superior frontal gyrus, the anterior cingulate cortex, the posterior cingulate cortex, Heschl's gyrus on the right, the left superior temporal gyrus and the middle temporal gyrus bilaterally (see Table 3).

Control–RVIP. This comparison produced significant rCBF decreases similar to the decreases noted above in the RVIP–rest comparison. Specifically, these were in the medial/superior frontal gyrus, Heschl's gyrus on the right, and the middle temporal gyri bilaterally.

Effect of presentation speed (standard–fast). There were no significant rCBF decreases produced by this comparison.

Effect of increasing working memory load (two digit–three digit). There were no significant rCBF decreases produced by this comparison.

Table 2. Stereotactic co-ordinates (from [52]) of maximal regional increases of rCBF when all four RVIP tasks were collectively compared with the control condition*

Anatomical area	*x*, *y*, *z* co-ordinates (mm)	Brodmann's area	*Z*-score
Fusiform gyrus (L)	−42, −64, −12	19	6.33
Fusiform gyrus (R)	42, −64, −12	19	4.93
Middle occipital gyrus (L)	−38, −76, −8	19	5.24
Middle occipital gyrus (R)	38, −64, −4	19	4.52
Inferior parietal gyrus (L)	−30, −54, 40	40	4.28
Superior parietal gyrus (R)	22, −68, 32	7	5.03
Supplementary motor area	0, 8, 52	6	4.31
Frontal cortex (L)			
Inferior gyrus	−44, 2, 32	44	6.13
Middle gyrus	−48, 14, 28	9	5.01

*The *Z*-score is a measure of significant change, with the threshold for significance being set at $Z > 4.20$ ($P < 0.05$ corrected for multiple comparisons).

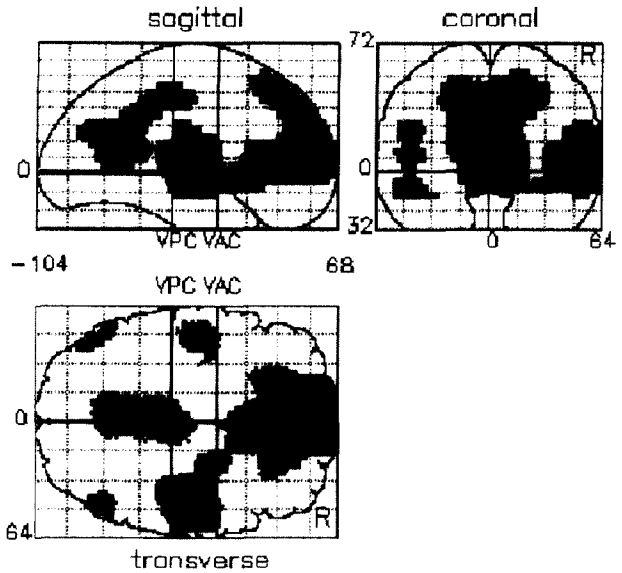

Fig. 4. Statistical parametric map (SPM) showing task-induced decreases in rCBF when all RVIP tasks are compared to rest (eyes closed). Significant pixels ($Z>4.20$) are displayed in sagittal, coronal and tranverse sections for each comparison (R = right hemisphere).

Correlational analysis

Task performance correlated negatively with rCBF change in bilateral occipital cortex/fusiform gyrus (x-, y- and z-co-ordinates = -44, -76, -12; $Z=5.76$, $P<0.0001$ on the left, and x-, y- and z-co-ordinates = 42, -76, -12; $Z=5.72$, $P<0.0001$ on the right). Additional activations were noted in the left inferior frontal cortex/precentral gyrus ($Z=3.90$, $P<0.0001$ uncorrected for multiple comparisons) and the pulvinar region of the left thalamus ($Z=3.29$, $P<0.001$ uncorrected for multiple comparisons). Positive correlations between task performance and rCBF were found in the right middle temporal gyrus ($Z=3.50$, $P<0.0001$ uncorrected for multiple comparisons) and the precuneus/posterior cingulate ($Z=3.17$, $P<0.001$ uncorrected for multiple comparisons).

Comparison of right- and left-handers

When the left- and right-handed subjects were compared in a between-subjects analysis, no significant differences of rCBF were found for any of the above comparisons.

Discussion

In comparison with rest (eyes closed), the RVIP task produced significant bilateral rCBF increases in the inferior frontal gyrus, parietal cortex, fusiform gyrus, and supplementary motor area (SMA), and also a lateralized right-sided activation in superior frontal gyrus rostrally. However, in comparison with the control task of simple visual sustained attention, the aforementioned right frontal activations (both inferior and superior gyrus) were no longer significant at the more rigorous threshold [compare Fig. 3(a) and (b)]. Decreases of rCBF in the medial and superior frontal gyrus, posterior cingulate and primary auditory cortex were observed for both of these comparisons. A comparison of two-digit vs three-digit sequences failed to produce any significant changes of rCBF, but a comparison of fast vs standard speed presentations produced significant activations in the lateral occipital cortex. There were no detectable differences of rCBF between right- and left-handers in the activations produced by the RVIP task.

Functional characterization of each of the aforementioned areas of rCBF change may help in the interpretation of psychopharmacological studies employing the RVIP, and related, tasks. The RVIP task comprises several distinct cognitive components: for example,

Table 3. Stereotactic co-ordinates (from [52]) of maximal regional *decreases* of rCBF when all four RVIP tasks were collectively compared with rest*

Anatomical area	x, y, z co-ordinates (mm)	Brodmann's area	Z-score
Temporal cortex (L)			
Middle gyrus	-46, -68, 24	39	4.21
Superior/middle gyrus	-44, -6, -8	12/21	4.71
Middle temporal gyrus (R)	46, -68, 24	39	5.01
Posterior cingulate	-2, -60, 12	23/31	6.00
Heschl's gyrus (R) (primary auditory cortex)	42, -26, 12	41	6.69
Frontal cortex (L)			
Medial gyrus	-6, 52, 4	10	6.72
Superior gyrus	-10, 52, 28	9	6.20
Anterior cingulate	-2, 46, 0	32	6.90

*The Z-score is a measure of significant change, with the threshold for significance being set at $Z>4.20$ ($P<0.05$ corrected for multiple comparisons).

sustained attention, selective attention, and working memory as outlined earlier. Previous neuropsychological investigations, both with normal volunteers and patients with lesions to the frontal cortex, have implied a role for the right frontal cortex in simple sustained attention [25, 56, 58, 59]. Previous PET studies have corroborated these findings, linking activation of the right frontal cortex to performance of sustained attention tasks in the visual, auditory and somatosensory modalities [10, 39]. Our own findings highlight this, with the relative absence of right superior and inferior frontal gyrus rCBF increases when the RVIP task was compared with the simple visual sustained attention control task. It should be noted, however, that while the inferior frontal activations are in a similar (though slightly more posterior) area to those identified by Pardo *et al.* [39], the more rostral frontal activation has not as yet been identified with sustained attention.

Robertson *et al.* [47] have demonstrated recently the influence of a non-spatial sustained attention system (possibly instantiated in the frontal cortex) on the spatial attentional systems involved in unilateral neglect (most certainly including the right posterior parietal cortex [30, 37, 46]). Neglect patients who had been trained to sustain attention more effectively showed significant performance benefits on novel tests of neglect, but not on control tests of working memory or spatial perception. This study illustrates the existence of multiple attentional systems, possibly involving anatomically discrete regions of the brain, which can be co-activated during performance of a single attentional task. In our study, selective attention for complex target sequences and/or their manipulation in working memory are two cognitive processes required over and above those needed for control task (sustained attention) performance. The relative absence of right frontal cortex activations when all RVIP tasks were compared with the sustained attention control reinforces the notion that the contribution of this region is to sustaining attention over time, rather than to selective attention or working memory.

The right rostral superior frontal gyrus activation is in a similar location to the rostrolateral frontal area reported by Baker *et al.* [6], who suggested that this area may be associated with the central executive processes of working memory, as indexed by a comparison of hard and easy problems in the Tower of London test of planning. However, the evidence obtained here suggests that this area may in fact have a computationally simpler role in vigilance or sustained attention. Another possibility is suggested by Baker *et al.* [7], who note activation of this area in several paradigms requiring simple verification or 'checking' behaviour, such that targets are compared with a pre-defined standard. In addition, Fletcher *et al.* [20] have also suggested that the verification processes involved in retrieval [51] engage the right frontal cortex, albeit more dorsally than the activation noted in the present study. Checking of a target to a standard is common to both the control and RVIP tasks, and indeed to almost all types of vigilance task. Therefore, the right rostral frontal area may subserve this particular component of sustained attention performance.

As mentioned previously, sustained attention paradigms have often been associated with fronto-parietal function [36, 39, 45], and our results confirm these findings. However, these studies suggest a laterality for sustained attention to the right hemisphere, whereas we have noted bilateral fronto-parietal activations. This apparent discrepancy may be accounted for by the greater complexity of the RVIP task, compared with other simple sustained attention tasks, in that verbal working memory is required for RVIP performance. Petrides *et al.* [43] reported bilateral prefrontal cortex activations in response to verbal working memory tasks, although bilateral *parietal* activations, which correspond closely to the rCBF increases found in this region by our study, were found also but were not commented upon. The task used by Petrides *et al.* [43] was non-spatial in nature, as is the RVIP task, and therefore the parietal lobe activations cannot simply be attributed to visuospatial processing. A recent PET study by Paulesu *et al.* [42] has delineated a neural network for the phonological loop component of working memory [3] in the left inferior parietal cortex and bilaterally in Broca's area (inferior frontal gyrus). Since subjects are more likely to rehearse digit sequences sub-vocally during the RVIP task, compared with the control task, the most parsimonious explanation for the left fronto-parietal activations seen in the comparisons of the RVIP task to both rest *and* the control condition is that of neuronal activation in the phonological loop. Digit sequences may be rehearsed sub-vocally (activating the inner speech articulatory control processes of the phonological loop) while two or three digits are held 'on-line' for comparison to a target template (activating the phonological store component of the phonological loop, thought to hold speech-based information).

It is possible, however, that subjects may employ their visuospatial sketchpad [3], rather than phonological loop, to hold digits on-line. In a preliminary study, Paulesu [21] has localized the visuospatial buffer to the right inferior parietal lobe, and the activations in this area in our own study may reflect this type of cognitive processing. However, selective attention is another important component of RVIP performance as described earlier, and many investigations with neurosurgically lesioned patients, and more recently imaging studies with healthy volunteers, have suggested a role for the parietal cortex, particularly on the right, in this form of attention [53]. It is possible, therefore, that the right parietal activations seen in this study may be related to the selective attention components of the task. However, our data preclude a definitive conclusion being made and a more explicit examination of this hypothesis should be undertaken in order to determine whether the parietal cortex is involved in non-spatial attention. It should be noted that the parietal cortex may be part of a 'posterior attentional network' [45], which also comprises the pulvinar nucleus of

the thalamus (suggested to engage attention toward the stimulus whilst filtering out irrelevant stimuli), and also the superior colliculus in the midbrain (proposed to shift attention from one stimulus location to another). Activation of the thalamus, also present in both comparisons of the RVIP task to rest and to control, is consistent with the existence of this neural network for selective attention, and indeed LaBerge and Buchsbaum [34] have found evidence to support a role for the pulvinar nucleus of the thalamus in selective attention using PET.

One of the more novel contributions made by our study was the use of a semi-factorial design. This was an attempt to tease apart the functional anatomy of selected RVIP cognitive components, in order to ease interpretation of psychopharmacological studies using this test. Unfortunately, specific comparisons of the two working memory modifications failed to provide any significant activations. Furthermore, we do not find any evidence to support Cohen *et al.*'s [11] hypothesis that activations in the right inferior/middle frontal cortex are associated with non-spatial working memory, and we suggest that the results of Cohen *et al.* [11] may have been due to more fundamental attentional components of the task. It may be argued that our two- and three-digit tasks did not activate working memory processes, differentially explaining the lack of rCBF change. The behavioural data however, show significant differences in the accuracy with which the two tasks were performed, suggesting that the three-digit task did indeed impose greater demands on working memory processes. If working memory was maximally (and therefore equally) engaged by both two- and three-digit tasks, rCBF changes associated with working memory would be no different for these two tasks and, furthermore, a decline in performance would be predicted by the extra demands made by the three-digit task. Grasby *et al.* [27] have noted similar effects in a graded response auditory–verbal memory paradigm. While performance was changing maximally as task difficulty increased, rCBF was found to be changing minimally in areas activated by the memory task.

Comparing a fast stimulus presentation speed with a slower one did produce some clear rCBF increases in the lateral occipital cortex. Increasing stimulus presentation speed is known to promote a decrement in performance of vigilance tasks over time, which may be related to the amount of effort needed to perform the task [38]. For the purposes of this discussion, effort shall be defined as an increase in demands made on the series of computations necessary for task performance. As the RVIP task becomes more effortful (with increasing speed and working memory load), performance declines and there is a corresponding rCBF increase in occipital cortex and fusiform gyrus as revealed by the correlational analysis. The similarity of rCBF profiles in the fast–slow analysis and the correlational analysis suggests that they are measuring the same process. We suggest that these rCBF changes reflect the greater degree of non-specific effort needed to perform the RVIP task when both working memory load and speed of presentation are high. Significantly greater activation of a specific brain area with a hard, as opposed to an easy, version of the same task has been reported already by D'Esposito *et al.* [18] and our data corroborate this pattern of results.

Recent PET data have suggested a functional dissociation in dorsal and ventral fusiform gyrus with regard to the processing of object and spatial information, respectively [12, 29]. The non-spatial nature of the RVIP task would predict rCBF increases of the ventral fusiform gyrus in a comparison of RVIPs with rest, and this was indeed observed. Supplementary motor area activation is present also in the comparison of the RVIP task with rest as well as control, although to a lesser degree in the latter comparison. This area is engaged by motor response preparation, particularly for those movements which have not been prompted by an explicit external stimulus [26, 41]. This process would appear to be recruited more in the RVIP tasks than the control task, since the former requires a constant background readiness to respond, as in the control task, but additionally may invoke motor preparation as soon as the initial digit of any target sequence (i.e. 2, 3, 4 or 5) is presented on the screen. The subject is immediately primed to respond in case the initial digit should be followed by subsequent members of the target sequence, and since presentation of these numbers occurs approximately four times as often as a target sequence, SMA activations are likely to be strong.

The decreases of rCBF are consistent with those reported previously for other PET cognitive activation paradigms. The deactivation of both primary auditory cortex and posterior cingulate (thought to be required for somatosensory processing [54]) has also been found in a task requiring visual selective attention to faces and locations [29]. The authors suggest that "selective attention to one sensory modality appears to be associated with suppressed activity in cortical areas that process input from other sensory modalities" and that this suppression may be subcortical in origin. Drevets *et al.* [19] recently came to a similar conclusion using a somatosensory PET paradigm. The medial and superior frontal/anterior cingulate deactivations have been noted in a number of paradigms, encompassing tests of motor learning, memory or 'executive' functions such as planning [6, 27, 31]. Conversely, rCBF *increases* in this area have been noted in the Stroop task, e.g. [8, 40], which requires subjects to divide attention equally between the stimulus itself (the name of the colour–word) and the response required to it (the colour of the ink). It seems that this cortical area may be deactivated when attention needs to be specifically directed and focused towards a prepotent goal or stimulus–response relationship, but is activated when attention needs to be distributed more widely.

To summarize, we have delineated a neuroanatomical network for performance of the RVIP task, which could be useful in interpreting the results of previous psy-

chopharmacological studies using the RVIP task. For example, cholinergic agents such as nicotine and scopolamine significantly alter RVIP performance in both healthy volunteers and patients with the classical posterior dementia, Alzheimer's disease. According to our results, cholinergic agents could be affecting RVIP performance through an action on frontal, parietal or fusiform/occipital areas. A recent PET study has shown that the muscarinic antagonist scopolamine attenuates memory-induced rCBF increases bilaterally in the frontal cortex [28], suggesting a possible site of action for a cholinergic modulation of RVIP performance. The noradrenergic agonist clonidine also has been found to impair performance of the RVIP task [14] and has been implicated in both attention and working memory [1, 2, 9, 14, 15]. We are currently employing a psychopharmacological PET paradigm in order to delineate the brain areas involved in the putative noradrenergic modulation of attention and/or working memory, using the RVIP task.

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