

# Context-dependent, neural system-specific neurophysiological concomitants of ageing: mapping PET correlates during cognitive activation

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## Summary

We used PET to explore the neurophysiological changes that accompany cognitive disability in ageing, with a focus on the frontal lobe. Absolute regional cerebral blood flow (rCBF) was measured in 41 healthy volunteers, evenly distributed across an age range of 18–80 years, during two task paradigms: (i) the Wisconsin Card Sorting Test (WCST), which depends heavily on working memory and is particularly sensitive to dysfunction of the dorsolateral prefrontal cortex (DLPFC); and (ii) Raven's Progressive Matrices (RPM), which may also have a working memory component, but depends more on visuo-spatial processing and is most sensitive to dysfunction of postrolandic regions. We used voxel-wise correlational mapping to determine age-related changes in WCST and RPM activation and developed a method to quantitate and localize statistical differences between the correlation maps for the two task paradigms. Because both WCST and RPM performance declined with age, as expected, correlational analyses were performed with and without partialling out the effect of task performance. Task-specific reductions of rCBF activation with age were found in the DLPFC during the WCST and in portions of the inferolateral temporal cortex involved in visuo-spatial processing during the RPM. We also found reduced ability to suppress rCBF in the right hippocampal region during

the WCST and in mesial and polar portions of the prefrontal cortex during both task conditions. Task-dependent alterations with age in the relationship between the DLPFC and the hippocampus were also documented; because the collective pattern of changes in the hippocampal–DLPFC relationship with ageing was opposite to that seen in a previous study using dextroamphetamine, we postulated a dopaminergic mechanism. These results indicate that, despite some cognitive overlap between the two tasks and the age-related cognitive decline in both, many of the changes in rCBF activation with age were task-specific, reflecting functional alteration of the different neural circuits normally engaged by young subjects during the WCST and RPM. Reduced activation of areas critical for task performance (i.e. the DLPFC during the WCST and posterior visual association areas of the inferolateral temporal cortex during the RPM), in conjunction with the inability to suppress areas normally not involved in task performance (i.e. the left hippocampal region during the WCST and mesial polar prefrontal cortex during both the WCST and RPM), suggest that, overall, reduced ability to focus neural activity may be impaired in older subjects. The context dependency of the age-related changes is most consistent with systems failure and disordered connectivity.

**Keywords:** ageing; brain activation; cognition; frontal lobe; PET

**Abbreviations:** BA = Brodmann area; DLPFC = dorsolateral prefrontal cortex; rCBF = regional cerebral blood flow; RPM = Raven's Progressive Matrices; RPMc = control task for RPM; WCST = Wisconsin Card Sorting Test; WCSTc = control task for WCST

## Introduction

It is generally accepted that normal ageing is associated with decline of certain higher cognitive functions. Notwithstanding wide individual differences, elderly individuals show a cognitive pattern characterized by performance decrements on memory tasks and on tests involving abstract reasoning, problem solving, visuospatial skills and selective attention (for reviews, see Botwinick, 1984; Craik and Jennings, 1992). Most investigators also find that cognitive behaviours specifically linked to the prefrontal cortex, including working memory, mental flexibility and response to external feedback, are particularly affected by the ageing process (Belleville *et al.*, 1996, for review, see Hochanadel and Kaplan, 1994) and that signs of prefrontal impairment, such as perseveration, may appear (Offenbach, 1974; Morris *et al.*, 1990; Daigneault and Braun, 1993).

Consistent with the notion of particular prefrontal involvement in ageing is the fact that a number of functional brain imaging studies have shown reduced blood flow and/or glucose metabolism in the prefrontal cortex (Kuhl *et al.*, 1984; Pantano *et al.*, 1984; Devous *et al.*, 1986; Martin *et al.*, 1991; Waldemar *et al.*, 1991). However, neither the functional neuroimaging nor the neuropsychological literature is without controversy. Both Duara *et al.* (1983) using PET and Yoshii *et al.* (1988) with SPECT failed to confirm reduced prefrontal cortical activity in older subjects. Neuropsychologically, age-related cognitive decline has received a variety of explanations, some focusing on prefrontally related constructs and others not. These have included primary reduction of working memory capacity (Light, 1982), general cognitive slowing (Salthouse, 1990) or decreased attentional abilities probably due to failure of inhibitory processes that control access to relevant information and removal of irrelevant information (Hasher and Zacks, 1988; Richardson, 1996). Thus, the exact nature of the cognitive decline that accompanies ageing, and its neural substrate, have remained unclear.

Recent PET studies of brain activation during cognition have demonstrated the utility of integrating neuropsychological and neurophysiological investigations of the cognitive sequelae of the ageing process (Grady *et al.*, 1994, 1995; Cabeza *et al.*, 1997a). These studies have reported that age-related cognitive changes are accompanied by altered cerebral activation in temporo-occipital and parietal extrastriate regions during tasks of visuospatial processing (Grady *et al.*, 1994), and in medial temporal/hippocampal areas during tasks of memory encoding and retrieval (Grady *et al.*, 1995; Cabeza *et al.*, 1997b), suggesting that important pathophysiological underpinnings of age-related cognitive changes may lie in shifts in the *pattern* of neural activation rather than, or perhaps in addition to, altered absolute global or regional activity. In addition, the alterations in prefrontal activation reported in older subjects collectively suggest that the qualitative nature of the changes is fluid and depends upon the behaviour during the scan: increased prefrontal

activation was found both during face and location processing (Grady *et al.*, 1994) and during memory recall (Cabeza *et al.*, 1997a), while reduced prefrontal activation was reported during memory encoding (Grady *et al.*, 1995; Cabeza *et al.*, 1997b).

In the present study, to explore age-related changes in prefrontal function, we measured cognitive activation with PET regional cerebral blood flow (rCBF) in 41 carefully screened healthy subjects evenly distributed over an age range of 18–80 years during performance of a task, the Wisconsin Card Sorting Task (WCST), which appears to depend heavily on working memory (Goldman-Rakic, 1987; Berman *et al.*, 1995) and to be particularly sensitive to dysfunction of the dorsolateral prefrontal cortex (DLPFC) (Milner, 1963; Luria, 1973). We mapped anatomical areas of significant correlation between age and neurophysiological activation related to performing the WCST and statistically compared these correlative results for the WCST with those during another abstract reasoning and problem-solving task, Raven's Progressive Matrices (RPM). Like the WCST, RPM may have a working memory component (Carpenter *et al.*, 1990; Prabhakaran *et al.*, 1997), but it appears to depend more upon visuospatial processing and computational problem solving and to be most sensitive to lesions and dysfunction of postrolandic regions rather than of the prefrontal cortex (Basso *et al.*, 1973). We hypothesized, therefore, that participation of the prefrontal cortex and other related regions in the two tasks could have different cognitive and neurobiological import and that the neurophysiological manifestations of the ageing process would, thus, be different during the tasks.

## Material and methods

### Subjects

Forty-one healthy volunteers (20 men and 21 women) signed informed consent in accordance with the National Institutes of Health Institutional Review Board and Radiation Safety Committee guidelines. Subjects were evenly distributed among the age range of 18–80 years: five  $\leq$  20 years (three female, two male) and six (three female, three male) for each decade from 21 to 80 years. Mean age was  $45.5 \pm 19.7$  years ( $45.9 \pm 19.8$  years for men and  $45.2 \pm 20.1$  years for women). Subjects received on average 16 years of education. There was no correlation between subjects' age and years of education. Six subjects were left handed. Because cerebrovascular risk factors have been postulated to affect functional brain imaging results in ageing studies (Naritomi *et al.*, 1979; for reviews, see Dastur *et al.*, 1963; Meyer *et al.*, 1994), we carefully screened this cohort for history of past or present medical condition or pharmacological treatment that could have relevance for rCBF or metabolism, and for psychiatric or neurological disorders, including head trauma or substance abuse. MRI scans were also obtained

(double-echo sequence; repetition time, TR = 2000; echo time, TE = 20/80) and were reviewed for structural abnormalities by a neuroradiologist. Screening of subjects  $\geq 40$  years of age also included physical examination and laboratory tests to rule out hypertension, as well as pulmonary, cardiovascular, hepatic, haematological, renal and thyroid disorders. Subjects over 40 years (with two exceptions, aged 42 and 54 years, whose test data were not available) were also evaluated with the Mini-Mental State exam (Folstein *et al.*, 1975), and only those who scored  $\geq 28/30$  underwent a PET study. Subjects were required to abstain from caffeine and nicotine for 4 h preceding the PET study. Women receiving oestrogen replacement therapy were also excluded.

### PET scans

Individually fitted thermoplastic masks were used to minimize head movements. Data were acquired with a Scanditronix PC2048-15B PET scanner (15 contiguous slices per scan with spatial resolution 6–6.5 mm both in-plane and axially). Transmission scans were obtained with a rotating pin source of  $^{68}\text{Ga}/^{68}\text{Ge}$  and were used to correct for radiation attenuation through skull and brain tissue. Each patient underwent four PET scans, each following an i.v. bolus of  $\sim 42$  mCi of  $^{15}\text{O}$  water, in a single scanning session. Emission data were acquired in 16 frames over 4 min (12 frames of 10 s each and four of 30 s each). Scan data were corrected for scatter, random coincidences and deadtime. Arterial input functions were measured with automated arterial blood sampling (Daube-Witherspoon *et al.*, 1992), and absolute rCBF (ml/min/100 g) was calculated with a rapid least squares method (Koepp *et al.*, 1985) as described elsewhere (Esposito *et al.*, 1996).

### Cognitive conditions

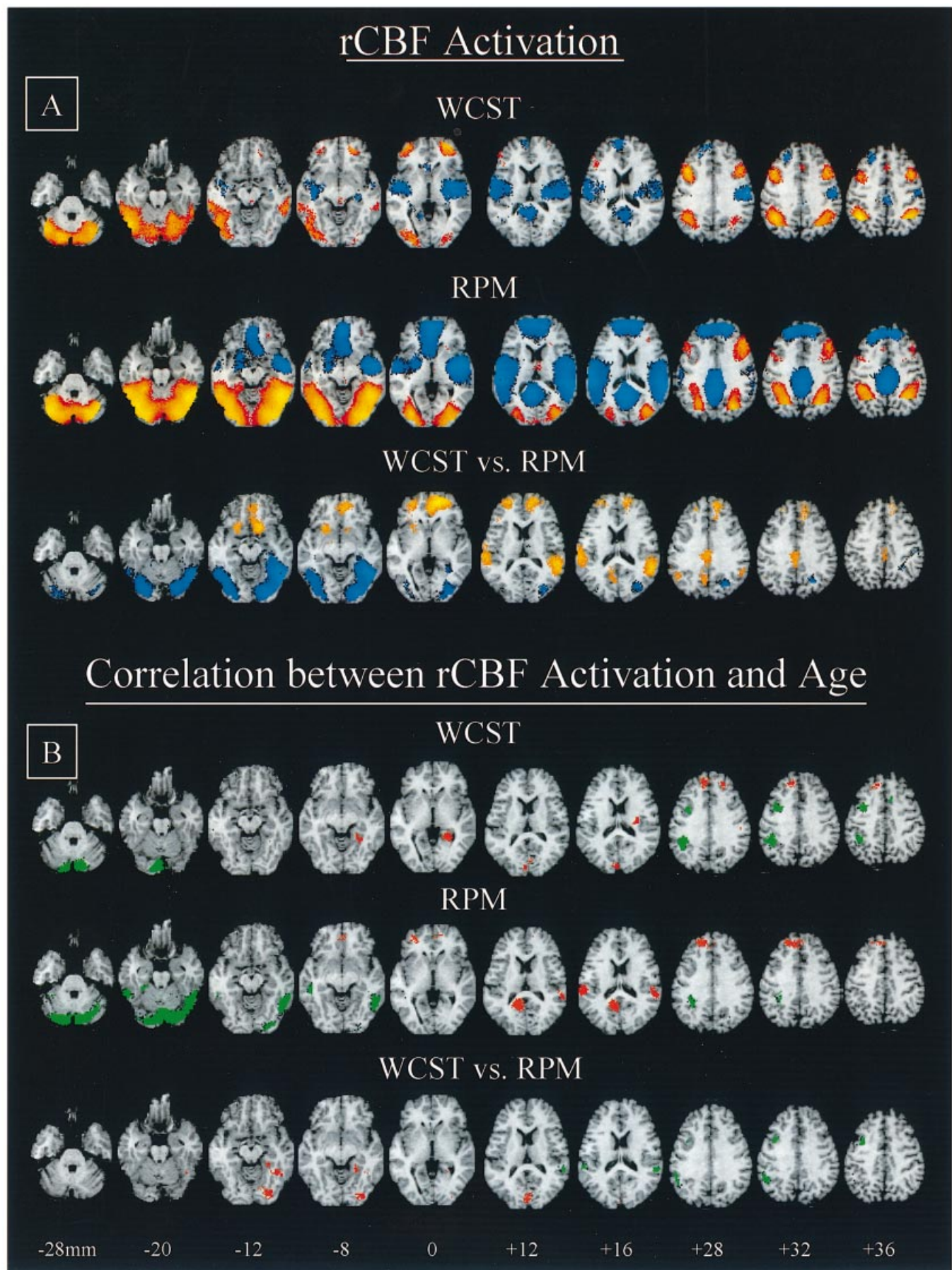
Subjects were administered four different cognitive tasks, one per scan: the WCST, RPM and their respective sensorimotor control tasks (WCSTc and RPMc) (see Berman *et al.*, 1988, 1995). The sensorimotor control tasks were designed to match the WCST and the RPM for visual stimulation and response modality but did not involve higher order cognitive processing and abstract reasoning. All tasks were begun 1 min before the injection of tracer and continued throughout the 4 min of the scan. Subjects responded using a button-pressing device held in the right hand during the WCST and the WCSTc. During RPM and RPMc, they verbally reported the number of the chosen response. Tasks were presented in counterbalanced order on a computer screen. The tasks were self-paced in order to engage the neurophysiological 'duty cycle' fully by avoiding non-cognitively occupied time during the measurement period. Subjects were told to concentrate on the task and to try their best. For both tasks, the percentage of correct to total responses was calculated as the cognitive outcome measure.

### The Wisconsin Card Sorting Task (WCST)

The WCST is a problem-solving, abstract reasoning task involving working memory (Goldman-Rakic, 1987; Berman *et al.*, 1995). It has been shown to be particularly sensitive to dysfunction of the prefrontal cortex (Milner, 1963; Luria, 1973), although its specificity has been questioned (Mountain and Snow, 1992), and it is known to activate prefrontal cortex physiologically as well as an associated network of regions including the inferior parietal lobule and the inferior posterior temporal lobe (Berman *et al.*, 1995). During our computerized WCST, subjects were required to match a central target stimulus to four surrounding reference stimuli on the basis of three possible abstract categories: colour, shape and number (for sample stimuli, see Berman *et al.*, 1995). Subjects must not only discover the three correct matching principles, they must also determine which is correct by using feedback displayed on the screen that indicates whether each response is right or wrong, maintain the rule through 10 trials, and then use feedback to shift to a new category after it is changed by the experimenter without warning to the subject. The ability to create an internal representation of the results of previous trials and then to use the internal representation as feedback to formulate a strategy for present and future responses, as well as the ability to shift abstract categorization when needed, are critical for good performance and have all been linked to the prefrontal cortex (Goldman-Rakic, 1987; Berman *et al.*, 1995). Previous studies have shown that ageing is associated with reduced performance on the WCST (Whelan and Leshner, 1985; Daigneault and Braun, 1993; Nagahama *et al.*, 1997). The sensorimotor control task for the WCST was a no-delay, matching-to-sample task which was of a visual complexity similar to the WCST. Subjects matched each central target stimulus to one of four unchanging surrounding reference stimuli (for sample stimuli, see Berman *et al.*, 1995).

### RPM

RPM is an abstract reasoning task first developed in 1938 (Raven, 1938). It is widely regarded as a good indicator of general intelligence (Jensen, 1982) and has found particular utility in patient populations in whom non-verbal tests are desirable. As with the WCST, there is evidence that performance on the RPM declines in older subjects (for reviews, see Burke, 1985; Salthouse, 1992). During RPM performance, subjects are shown patterns in a  $3 \times 3$  cell matrix with a missing piece [see, for example, Raven (1938); Carpenter *et al.* (1990) for sample stimuli]. They are required to determine which of six to eight possible alternatives best completes the matrix so that the interrelational rules among the elements (e.g. along the rows and the columns) are satisfied. Good RPM performance requires that subjects perceive the relationships between cells in the matrix, determine the relationships between the columns and rows of the matrix and then integrate this information. A crucial



difference between the RPM and the WCST is that while the WCST depends heavily upon internal representations of previous trials and the current conceptual set, all the information necessary to solve each RPM trial is available externally to the subject throughout that trial. The correct answer does not depend on the results of previous trials as does the WCST. While it has been argued alternatively that the necessity of keeping several conceptual formulations in mind during RPM is itself a working memory function (Carpenter *et al.*, 1990) involving the prefrontal cortex (Prabhakaran *et al.*, 1997), studies of patients with lesions suggest that postrolandic structures may be more critical for this task (Basso *et al.*, 1973). The control task was a no-delay, matching-to-sample task. Subjects matched the reference stimulus displayed at the top of the screen to one of eight possible answer stimuli displayed on the bottom.

### Image processing

For each subject, the four PET scans were realigned with the program of Woods *et al.* (1992). The realigned PET images were roll–yaw corrected and then interpolated to 43 slices, spatially normalized into the stereotaxic space of the Talairach and Tournoux atlas (1988), and smoothed with a  $20 \times 20 \times 12$  mm filter in the  $x$ ,  $y$  and  $z$  dimensions, respectively, with the SPM95 package (Friston *et al.*, 1995). For the voxel-level analyses, we chose to use ratio normalization for global flow. This method assumes the existence of a proportional relationship between regional and global CBF values (Shimosegawa *et al.*, 1995), whereas ANCOVA normalization assumes an additive relationship (Friston *et al.*, 1990). Normalized images from the respective control tasks were subtracted from the WCST and the RPM to isolate rCBF activation linked to the higher cognitive processing during these two tasks. For voxel-by-voxel and correlational analyses, local maxima of the statistical results were found by searching within a volume of  $20 \times 20 \times 20$  mm ( $10 \times 10 \times 5$  voxels in  $x$ ,  $y$  and  $z$ ). Only those maxima representing volumes of  $>10$  contiguous voxels were considered further. Activation and correlational maps were thresholded at  $P < 0.005$  for purposes of illustration, but only those maxima significant at  $P < 0.001$  were tabulated and explored further with *post hoc* analyses.

Specific notations are made in the text where *post hoc* results that clarified the primary findings are reported at lesser significance.

### Statistical analysis

#### Effect of ageing on global CBF and cognitive performance

Age-related changes in task performance were evaluated with Pearson's correlation analysis. Pearson's correlation analysis was also used to explore the relationship between normal ageing and global CBF (determined as the average of all intracerebral voxels) for each of the four tasks. This was of interest given the fact that the literature is controversial with regard to the possibility of reduced global CBF (Dastur *et al.*, 1963; Shaw *et al.*, 1984; for a review, see Meyer *et al.*, 1994). Evaluation of age-related changes in global CBF is also important methodologically because most strategies for regional activation analysis depend on some method of normalization for intertask and intersubject differences in global flow, a procedure that potentially can produce artefactual findings if between-task or between-group global differences do exist.

#### rCBF activation in younger subjects

Prior to evaluating ageing effects on rCBF, we examined the data for the 20 younger subjects of our population (using a median split that yielded an age range of 18–42 years for this subgroup) to ensure that their patterns of regional activation were consistent with previous reports and to compare WCST and RPM activation directly. Mean performance scores for this young subcohort fell, for both the WCST and the RPM, within 1 SD of previous results obtained from larger populations of young control subjects (Ostrem *et al.*, 1993; Berman *et al.*, 1995). For the two cognitive paradigms, task and control were compared within statistical parametric maps (SPM) using weighted linear contrasts. The activation maps for the two paradigms were also statistically compared directly. Age-related changes in rCBF activation were interpreted in light of the pattern of regional activation in this younger group.

**Fig. 1** (A) rCBF activation in the younger group during the WCST (top row) and the RPM (middle row). Red/yellow indicates greater rCBF during the task (WCST or RPM) compared with the control (WCSTc or RPMc); blue indicates greater rCBF during the control (WCSTc or RPMc) compared with the task (WCST or RPM). The bottom row shows the comparison of rCBF activation between the WCST and the RPM paradigms. In red/yellow are shown areas in which the differences between task and control were greater during the WCST paradigm than during the RPM paradigm. In blue are shown areas in which the differences between task and control were greater during the RPM paradigm than during the WCST paradigm. (B) Voxel-by-voxel correlation maps between age and rCBF activation during the WCST (top row) and the RPM (middle row). Only those voxels in which the correlation exceeded a threshold of  $P < 0.005$  are highlighted. Red/yellow indicate areas where activation increased with age (positive correlations,  $P < 0.005$ ); green indicates negative correlations ( $P < 0.005$ ). The bottom row shows a voxel-by-voxel comparison of the age–rCBF correlations between the WCST and RPM paradigms conducted with Williams' test ( $P < 0.005$ ). Here, red/yellow indicate areas in which the correlation coefficient was greater during the WCST; in green are areas in which the correlation coefficient was greater during RPM. WCST = Wisconsin Card Sorting Test; RPM = Raven's Progressive Matrices; rCBF = regional cerebral blood flow.

### Voxel-based correlations between age and rCBF activation

We took advantage of the even age distribution of our cohort to search for linear relationships between rCBF activation and age. For the WCST and RPM paradigms, voxel-by-voxel Pearson's Product Moment correlation analyses were performed between age and normalized rCBF activation (task minus control) using software developed by our group at the NIMH (T.M.E., J.D.V.H. and G.E.). Local maxima of regions with significant correlations were investigated further within the context of the standard task-related rCBF changes in the younger group by tabulating for each task (i) the direction, correlation coefficient and significance level of the age-rCBF correlation and (ii) the direction and significance of the rCBF activation (task minus control) at that locale in the younger and older subgroups. Because we anticipated a decline in performance with age which could, itself, affect rCBF activation, and because our primary goal was to test the impact of age on rCBF activation, we also examined areas with significant age-activation correlations after partialling out the effect of performance (% correct responses). We further explored with multiple regression analysis whether the variance in rCBF activation in these regions was accounted for better by age, by performance or by age and performance level together.

Finally, the crucial step of this experiment was to determine whether significantly different neurophysiological correlates of ageing were demonstrated during the two tasks. To test this hypothesis, we statistically compared, on a voxel-by-voxel basis, the correlation coefficients between age and WCST activation with those between age and RPM activation. For this purpose, we used a voxel-wise version (T.M.E., J.D.V.H. and G.E.) of Williams' test (Williams, 1959). Williams' test is a well-validated statistical approach for assessing the equality of two correlation coefficients that are dependent (as they are in this experiment, since the WCST and RPM rCBF data were collected from the same sample) (Neill and Dunn, 1975; Steiger, 1980). Williams' statistic has the shape of a  $t$ -distribution with d.f. =  $n-3$ , and its mathematical representation is given by:

$$T_2 = (r_{jk} - r_{jh}) \{ (n-1)(1 + r_{kh}) / [2(n-1/n-3)|R| + r^2(1-r_{kh})^3] \}^{1/2};$$

where, in our case,  $r_{jk}$  represents the matrix for the correlation between age ( $j$ ) and WCST activation ( $k$ ),  $r_{jh}$  represents the matrix for the correlation between age ( $j$ ) and RPM activation ( $h$ ) and  $r_{kh}$  represents the matrix for the correlation between WCST ( $k$ ) and RPM activation ( $h$ ). The latter takes into account any correlation between WCST and RPM rCBF activation data.

$$|R| = (1 - r_{jk}^2 - r_{jh}^2 - r_{kh}^2) + (2r_{jk}r_{jh}r_{kh})$$

is the determinant of the  $3 \times 3$  correlation matrix containing the coefficients being tested; and  $r^2$  is expressed as  $1/2(r_{jk} + r_{jh})$ .

Voxels with significant Williams' test were mapped onto

a representative MRI also spatially normalized to Talairach space. The direction, magnitude and significance level of each local maximum in this correlational difference map were examined.

## Results

### Effect of ageing on global blood flow and cognitive performance

There was a significant negative correlation between age and percentage correct for both the WCST ( $r = -0.53$ ,  $P < 0.001$ ) and RPM ( $r = 0.58$ ,  $P < 0.001$ ), but not for the control tasks. Mean % correct scores  $\pm$ SD for the young and the old group were, respectively:  $76.1 \pm 12.5$  and  $56.4 \pm 19.0$  during the WCST, and  $85.2 \pm 13.1$  and  $61.1 \pm 22.4$  during the RPM. No significant effect of ageing on global CBF was found for any of the four tasks (WCST:  $r = -0.24$ ,  $P = 0.14$ ; WCSc:  $r = -0.22$ ,  $P = 0.16$ ; RPM:  $r = -0.14$ ,  $P = 0.38$ ; RPMc:  $r = -0.03$ ,  $P = 0.83$ ).

### CBF activation in younger subjects

In our younger subjects, the patterns of regional activation for both the WCST and the RPM (Fig. 1A, top two rows) were consistent with earlier studies (Ostrem *et al.*, 1993; Berman *et al.*, 1995; Mattay *et al.*, 1996). There were a number of similarities between the two tasks. Both activated the dorsolateral [Brodmann area (BA) 9 and 46] prefrontal cortex, inferior parietal lobule (BA 39/40), anterior cingulate, and inferolateral temporal (BA 21 and 37) and occipital (BA 18/19) cortex bilaterally. In both tasks, relative deactivations were found in mesial polar portions of the prefrontal cortex (BA 10), perisylvian areas of the superior temporal and inferior temporal lobe (BA 38 and 22) and the posterior cingulate (BA 23/31).

Important differences between the two tasks were also observed (Fig. 1A, bottom row). The WCST activated a ventral and more anterior area of the prefrontal cortex (BA 10 and 47) that was not activated by RPM (between-task comparison,  $P < 0.0001$ ), while RPM activated visually associated areas including BA 18, 19 and 37 more than the WCST ( $P < 0.001$ ). Portions of the inferior parietal lobule (BA 39) and the inferior temporal lobe (BA 20/21) were activated more by the WCST (between-task comparison  $P < 0.0001$ ). The right hippocampal/parahippocampal region was activated by RPM but not by the WCST (between-task comparison,  $P < 0.005$ ).

### Correlations between age and rCBF activation

#### The Wisconsin Card Sorting Task (WCST) paradigm

During the WCST paradigm (Fig. 1B, top row, and Table 1), there were a number of areas in which there was reduced activation as a function of increasing age

**Table 1** Wisconsin Card Sorting Test

		BA	Coordinate			<i>r</i>	<i>P</i>	Activation in young		Activation in old	
			<i>x</i>	<i>y</i>	<i>z</i>			<i>Z</i>	<i>P</i>	<i>Z</i>	<i>P</i>
Negative correlations between rCBF change and age											
Anterior cingulate	R	32	10	8	44	−0.5	<0.001	1.79	<0.05	−2.71	<0.005
Frontal–dorsolateral	L	9	−32	4	36	−0.59	<0.0001	3.30	<0.001	−1.06	NS
Parietal–inferior lobule	L	39/40	−40	−52	32	−0.55	<0.001	4.17	<0.0001	0.66	NS
Cerebellum–midline	R		4	−88	−28	−0.58	<0.0001	3.32	<0.001	−1.51	NS
Cerebellum–posterior	L		−18	−96	−24	−0.6	<0.0001	2.45	<0.01	−2.14	<0.05
Positive correlations between rCBF change and age											
Frontal–mesial polar	L	9	−8	56	24	0.6	<0.0001	−4.16	<0.0001	2.27	<0.05
Frontal–lateral polar	R	9	20	42	28	0.51	<0.001	−1.46	NS	2.49	<0.01
Occipital–cuneus	L	18	−4	−96	16	0.5	<0.001	−0.99	NS	2.82	<0.005
Occipital–cuneus	R	17	8	−78	12	0.5	<0.001	−2.46	<0.01	1.38	NS
Parahippocampal	R	30/19	26	−50	−4	0.55	<0.001	−1.83	<0.05	2.95	<0.005

Performance expressed in % correct responses; L = left; R = right; BA = Brodmann area; *x*, *y*, *z* = stereotaxic coordinates; *x* = medial–lateral distance from the middle (positive = right); *y* = anterior–posterior distance relative to the anterior commissure (positive = anterior); *z* = superior–inferior distance from the intercommissural line (positive = superior); NS = not significant.

(i.e. negative correlations between age and rCBF activation; in all cases  $P \leq 0.001$ ,  $r \leq -0.5$ ). These occurred exclusively in regions that were activated by the younger subjects (Fig. 1A, top row, and Table 1): left DLPFC, left inferior parietal lobule, right anterior cingulate and cerebellum. These correlations mainly reflected an actual reversal of the quantitative relationship between the WCST and its sensorimotor control task: areas activated by the WCST in younger subjects showed relatively less activity during the WCST relative to the control task in older subjects (Table 1).

In contrast, significant increases in activation with age ( $P \leq 0.001$ ;  $r \geq 0.5$ ) occurred in regions where there was no activation or even apparent deactivation (i.e. control > task) in the younger group (Fig. 1B, top row, and Table 1). These included left mesial and right lateral portions of the polar prefrontal cortex, the cuneus and the right parahippocampal gyrus. These correlations also mainly reflected an actual reversal in the relationship between the task and its control (see Table 1): areas normally deactivated by the younger subjects became activated by the older subjects, particularly the mesial and lateral portions of the polar prefrontal cortex, and the parahippocampal gyrus.

Partial correlations showed that the associations between age and rCBF activation largely remained significant at the  $P < 0.005$  level when performance was covaried out. The only exception was the positive correlation in the right polar prefrontal cortex which retained the direction of the relationship but became less robust ( $P < 0.05$ ). Multiple regression analysis showed that the addition of performance level to age as an independent variable could not explain a significantly greater portion of the variance of rCBF activation in these regions than age alone.

### RPM paradigm

For the RPM paradigm (Fig. 1B, middle row, and Table 2), like the WCST, age-related reductions of rCBF activation (negative correlations) also occurred mainly in areas activated by the young subjects (Fig. 1A and Table 2): inferolateral temporal cortex including the fusiform gyrus bilaterally and the middle temporal gyrus on the left; portions of the left medial temporal cortex including the parahippocampal gyrus; the left inferior parietal lobule; and the cerebellum. Unlike the WCST, these negative correlations mainly represented areas in which older subjects showed reduced ability to activate regions normally involved in RPM performance, rather than reversals in the functional relationship between the task and control.

Positive correlations between age and activation (Fig. 1B, middle row, and Table 2) were found exclusively in areas normally deactivated in the younger group during RPM performance compared with the RPMc: left and right superior temporal gyri, left posterior cingulate and, as in the WCST, mesial and lateral portions of the polar prefrontal cortex. These findings reflected age-related diminution or disappearance of the relative deactivation. In other words, both the positive and negative correlations appear to represent, in general, an attenuation in the older subjects of the activation/deactivation pattern typically seen in the younger group.

Partial correlation analysis showed that the association between age and rCBF activation remained significant at the  $P < 0.005$  level when performance was covaried out. The only exception was the right mesiopolar prefrontal cortex, where the direction of the correlation remained the same but became less robust ( $P < 0.05$ ). As in the WCST, multiple regression analysis showed that the addition of performance level to age as an independent variable did

**Table 2** *Raven's Progressive Matrices*

			BA			Coordinate			<i>r</i>	<i>P</i>	Activation in young		Activation in old	
			<i>x</i>	<i>y</i>	<i>z</i>	<i>Z</i>	<i>P</i>	<i>Z</i>			<i>P</i>			
Negative correlations between rCBF change and age														
Parietal–inferior lobule	L	40	−30	−42	28	−0.53	<0.001	2.70	<0.005	−1.04	NS			
Temporal–fusiform	L	37	−50	−52	−24	−0.62	<0.0001	5.21	<0.00001	3.04	<0.005			
Temporal–fusiform	R	37	54	−58	−16	−0.62	<0.0001	5.71	<0.00001	3.33	<0.001			
Temporal–middle gyrus	L	21	−52	−32	−4	−0.51	<0.001	0.84	NS	−3.89	<0.0001			
Parahippocampal	L	36	−22	−48	−20	−0.51	<0.001	4.09	<0.0001	0.64	NS			
Cerebellum–midline	L		−4	−82	−28	−0.59	<0.0001	4.26	<0.0001	0.96	NS			
Cerebellum–lateral	R		28	−82	−28	−0.65	<0.0001	5.88	<0.00001	2.50	<0.01			
Cerebellum–lateral	R		−30	−84	−28	−0.62	<0.0001	5.04	<0.00001	2.98	<0.005			
Positive correlations between rCBF change and age														
Posterior cingulate	L	23	−12	−54	12	0.64	<0.0001	−5.52	<0.00001	0.93	NS			
Frontal–lateral polar	L	9	−18	48	28	0.58	<0.0001	−5.04	<0.00001	−2.75	<0.005			
Frontal–lateral polar	L	10	−24	46	0	0.51	<0.001	−2.57	0.01	0.48	NS			
Frontal–mesial polar	R	10	10	52	0	0.53	<0.001	−4.98	<0.00001	−2.46	<0.01			
Temporal–superior	L	22	−50	−36	16	0.58	<0.0001	−6.55	<0.00001	−3.81	<0.0001			
Temporal–superior	R	22	58	−42	16	0.55	<0.001	−5.72	<0.00001	−3.56	<0.001			

Performance expressed in % correct responses; L = left; R = right; BA = Brodmann area; *x*, *y*, *z* = stereotaxic coordinates; *x* = medial–lateral distance from the middle (positive = right); *y* = anterior–posterior distance relative to the anterior commissure (positive = anterior); *z* = superior–inferior distance from the intercommissural line (positive = superior); NS = not significant.

not explain a significantly greater portion of the variance of rCBF activation in these regions than age alone.

### Comparison of age–activation correlation maps for WCST and RPM paradigms

To evaluate statistically whether the neurophysiological correlates of ageing were different for the two tasks, we performed voxel-wise Williams' tests. This analysis (Fig. 1B, bottom row, and Table 3) revealed a number of regions in which the relationship between age and rCBF activation differed across the two tasks, suggesting that demonstrable neurophysiological correlates of ageing depend upon the neural systems required for the particular cognitive operations attempted. The left dorsolateral prefrontal cortex was activated by both tasks in the younger cohort, but activation decreased during the WCST only, and was actually deactivated in the older group (Fig. 2). In other cases, these cross-correlational differences occurred in areas where the activation patterns of the two tasks differed in the younger cohort (cf. Fig. 1A, bottom row, with bottom row of Fig. 1B). These included regions differentially activated across the two tasks in young subjects that were not brought on-line as robustly by the older subjects: right inferior occipital cortex and fusiform gyrus for RPM and left temporoparietal cortex for the WCST. Each of these represents a region whose activation is important for the particular task, but is reduced during that task in the older subjects (top two rows of Fig. 1B). There were also regions normally *not* a part of the task's activation circuit (i.e. regions not activated, or even deactivated by younger subjects), that were brought on-line, or were less deactivated, in a task-specific manner by the older subjects: the right cuneus and the right parahippocampal

area for the WCST and the right superior temporal cortex for RPM.

Our analyses also demonstrated some regions in which the effects of ageing on rCBF activation were similar across the WCST and RPM, as seen in the top and middle rows of Fig. 1B. Positive correlations in the polar portions of the prefrontal cortex (Fig. 2) and negative correlations in the cerebellum were found in both task paradigms, and did not differ according to Williams' test (Fig. 1B, bottom; Fig. 2, top and bottom right).

### Discussion

In our cohort, cognitive performance on both the WCST and RPM declined with age, a finding in agreement with previous studies of these and similar tasks (Burke, 1985; Whehlan and Leshner, 1985; Daigneault and Braun, 1993) and with the general notion that working memory, abstract reasoning and problem-solving abilities deteriorate in older subjects (Botwinick, 1984). Also in this cohort, age-related changes in rCBF activation were observed during both tasks even after correction for changes in performance, and significant across-task differences in the location and direction of the relationship between age and neurophysiological activation were found. We did not, however, detect a significant correlation between global CBF values and age for any of the four cognitive conditions. The absence of an age effect on global brain activity disagrees with some earlier studies demonstrating a reduction of global values with increasing age (Kuhl *et al.*, 1984; Shaw *et al.*, 1984; Grady *et al.*, 1990), but is consistent with others (Dastur *et al.*, 1963; Duara *et al.*, 1983; de Leon *et al.*, 1984) in which, like ours, subjects were screened carefully to exclude those with risk factors for

**Table 3** Statistical comparison of the age–rCBF activation correlations for the WCST and the RPM (Williams' test)

		Williams' test						Correlation between age and rCBF activation				Activation in young (Z)		Activation in old (Z)			
		BA			Coordinate			<i>r</i>	<i>P</i>	WCST		RPM		WCST	RPM	WCST	RPM
		<i>x</i>	<i>y</i>	<i>z</i>				<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>						
WCST > RPM																	
	Occipital–cuneus	R	18	2	−84	12	4.02	<0.001	0.45	<0.005	−0.16	NS	−1.30	0.30	1.78	−1.68	
	Occipital–inferior	R	18	28	−90	−8	3.92	<0.001	0.30	0.06	−0.44	<0.005	2.30	5.82	3.94	3.38	
	Parahippocampal	R	36	24	−50	−8	3.57	<0.001	0.46	<0.005	−0.19	NS	−1.01	3.32	2.92	1.85	
	Temporal–fusiform	R	37	38	−54	−12	3.56	<0.001	0.28	0.07	−0.36	<0.05	0.54	5.87	2.35	4.88	
RPM > WCST																	
	Frontal–dorsolateral	L	9	−32	4	36	3.76	<0.001	−0.59	<0.001	0.02	NS	3.31	1.97	−1.06	1.51	
	Temporal–superior	R	22	60	−44	12	4.59	<0.001	−0.21	NS	0.50	<0.001	0.08	−5.75	−2.29	−3.49	
	Temporoparietal	L	39	−48	−62	28	3.63	<0.001	−0.32	<0.05	0.34	<0.05	3.19	−1.91	0.48	0.09	

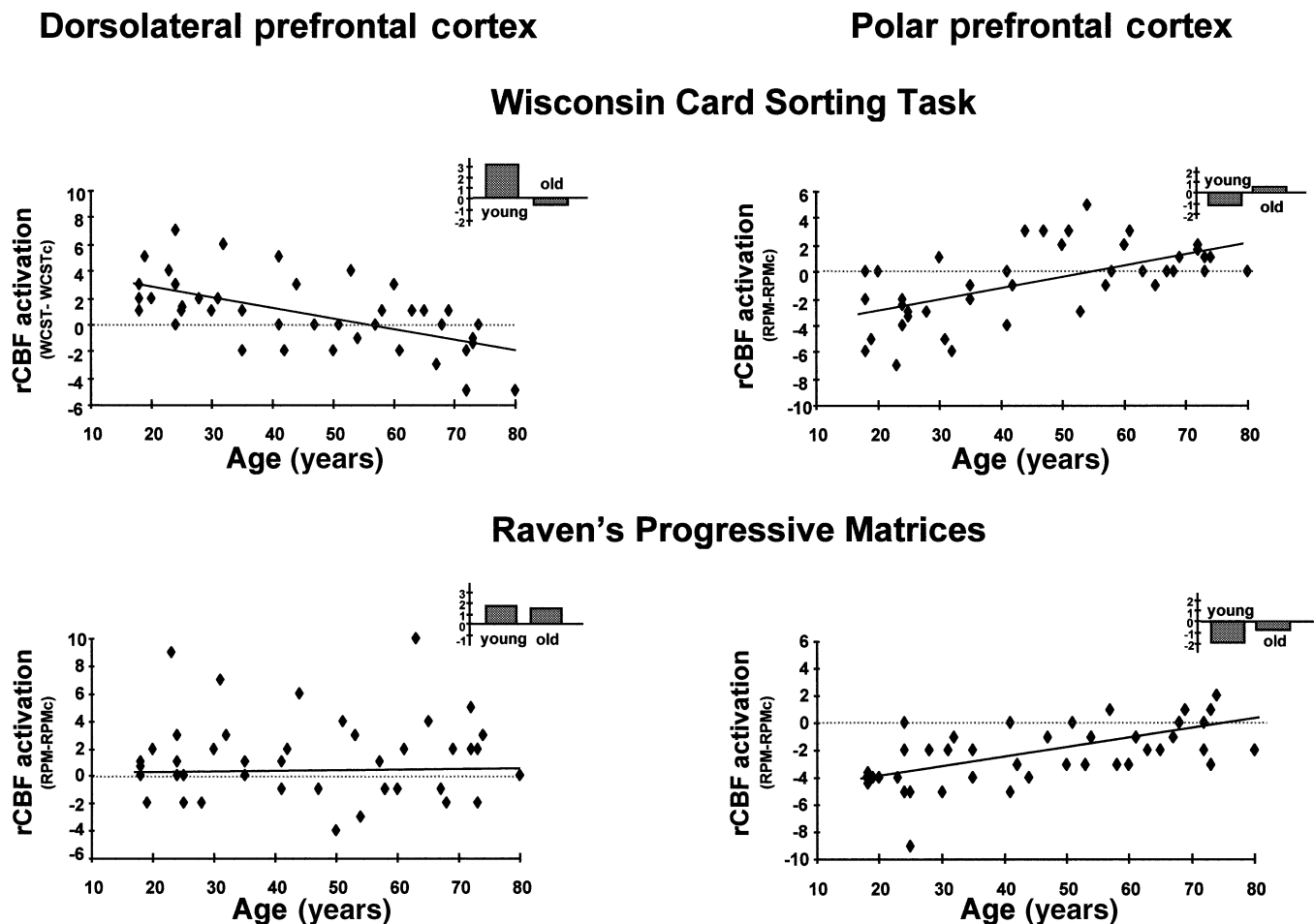
WCST = Wisconsin Card Sorting Test; RPM = Raven's Progressive matrices; L = left; R = right; BA = Brodmann area; *x*, *y*, *z* = stereotaxic coordinates; *x* = medial–lateral distance from the middle (positive = right); *y* = anterior–posterior distance relative to the anterior commissure (positive = anterior); *z* = superior–inferior distance from the intercommissural line (positive = superior); NS = not significant.

cerebrovascular disease. There is evidence that the presence of such factors accelerates the age-related decline in global values of CBF and glucose metabolism (for a review, see Meyer *et al.*, 1994).

The most important findings to emerge from this study were the correlations between age and rCBF activation and the across-task differences in this relationship. Technical reasons for these findings, particularly those that could be related epiphenomenologically to features of the ageing brain, must be considered. Although frank structural atrophy as well as less apparent neuronal loss are not uncommon in ageing, it is unlikely that these neurostructural changes played a role. First, we carefully excluded subjects with MRI evidence of microvascular disease, significant atrophy or other anatomical abnormality. Secondly, we found similar age–activation relationships in an earlier analysis of these data (Esposito *et al.*, 1995) in which stereotaxic normalization was not used and individual regions of interest were drawn on each subject's MRI, thereby minimizing the possibility of increased partial volume effects in the older subjects (due to more CSF-containing voxels being averaged with true brain tissue if subclinical atrophy were present). Thirdly, it is highly unlikely that partial volume effects could explain our several findings of *increased* activation with ageing, particularly where these represented actual reversals of the relationship between the task and its control, as seen for the WCST in the hippocampal/parahippocampal region; this region would be a likely candidate for partial volume effects, if they exist, because some investigators (de Leon, 1995), although not all (Sullivan *et al.*, 1995), have suggested it is particularly subject to neuronal loss with ageing. Finally, and perhaps most importantly, is our use of the within-subject, paired task activation method in which baseline sensorimotor and target tasks are compared. With this approach, non-specific effects of atrophy are likely to occur in the baseline task as well as the task of interest and will, therefore, be controlled for, an important advantage highlighted below.

Also, the across-paradigm statistical differences between the age–activation relationships that were found in several regions cannot be explained on the basis of atrophy.

The use of rCBF activation data (task minus control) has the crucial advantage of controlling for non-specific effects of ageing and focuses the analysis on changes in regional activity that are related to the specific effects of age on higher cognitive processing. However, this approach may make it difficult to conclude firmly that the task-specific age-related changes we have reported are related specifically to the cognitive aspects of the task, rather than the sensorimotor aspects of the experiment. To investigate this further, we tested, in those regions showing significant age–rCBF activation correlations (Tables 1 and 2) or significantly different age rCBF activation correlations across task (Table 3), whether similar relationships to age could also be found for unsubtracted rCBF measured during the WCST and RPM alone. For the two task paradigms considered separately, in all regions with negative correlations between age and rCBF activation (Tables 1 and 2), negative correlations at the trend level or greater were indeed also seen between age and rCBF during the WCST and RPM alone—with one exception, the left parahippocampal region during RPM. That these decreases with age could be demonstrated may link these changes more firmly to the cognitive aspects of the task, but also may not be surprising given the fact that the relationship between age and the activity of the grey matter as a whole is dominated by negative trends, as has been reported by others (for a review, see Meyer *et al.*, 1994). This regionally non-specific tendency for grey matter activity to decrease with age, probably due to microscopic structural changes throughout the brain (e.g. clinically inapparent neuronal loss), made it difficult to demonstrate in unsubtracted data most of the increases with age that were apparent in the activation data (task minus control). These positive correlations between age and brain function during the tasks were largely only apparent when viewed against the baseline of the sensorimotor



**Fig. 2** Plots of the correlations between rCBF activation (task minus control) and age for the left dorsolateral prefrontal cortex (left) and left polar prefrontal cortex (right) during the WCST (top) and RPM (bottom) paradigms; insets show the mean activation values (task – control) for the younger and older groups. In the left dorsolateral prefrontal cortex (left), activation decreased with age during the WCST (top left;  $r = -0.59$ ,  $P < 0.0001$ ; see also Table 1), whereas during RPM activation remained constant across the age span (bottom left;  $r = 0.02$ , NS). The mean values for the older and younger groups indicate that the negative correlation during the WCST represents a tendency in the older subjects to deactivate this normally activated region; in contrast, during RPM, there was virtually no difference in activation between younger and older groups. In the left polar prefrontal cortex (right), positive correlations were found during both the WCST (top right;  $r = 0.60$ ,  $P < 0.0001$ ) and RPM (bottom right;  $r = 0.58$ ,  $P < 0.0001$ ) (see also Tables 1 and 2). For both tasks, the older subjects showed less suppression of the polar prefrontal cortex than the young. During the WCST, polar prefrontal cortex tended to become activated compared with baseline in the older subjects, a reversal of the normal relationship between the task and its control. WCST = Wisconsin Card Sorting Test; WCSTc = Wisconsin Card Sorting Test control; RPM = Raven's Progressive Matrices; RPMc = Raven's Progressive Matrices control; rCBF = regional cerebral blood flow.

controls. In some cases, the relationship between the task and control actually reversed direction, while in others the neurophysiological differences between task and control became less; these relative changes can, themselves, be seen as another example of the task-dependent changes which we discuss below in the context of the different neural systems subserving our two cognitive tasks. We believe that the fact that age-related changes in the control task may also occur [as has been demonstrated for simple perceptual matching tasks (Grady *et al.*, 1994)] is another factor in favour of the paired task approach we used, in which any changes due to sensory or motor aspects of performing our tasks are 'baseline' out. It is thus important to emphasize that the within-task paradigm changes we report here occur relative to low

level sensorimotor tasks, which themselves may have age-related changes. However, because our two sensorimotor control tasks, both being no-delay match-to-sample tasks, require the same cognitive operations and differ only in response mode (motor for the WCSTc and verbal for the RPMc), we hypothesized that any age-related changes in them would have little effect in the across-task differences in the relationship between age and rCBF activation (Table 3), the crux of our experiment. We thus predicted that those results would be well supported by a Williams' test for across-task differences between the correlations of age and rCBF during the WCST itself, and of age and rCBF during the RPM itself (i.e. unsubtracted data). This prediction was born out: in every case listed in Table 3, except the superior

temporal cortex, Williams' test demonstrated differences between the correlations of age and unabstracted rCBF data for the WCST and RPM (albeit in some cases at lesser significance, probably due to better control of non-age-related variance and non-specific between-subject effects when the control task baselines are used). This result anchors the task-dependent nature of our neurophysiological results quite firmly to differences in the higher cognitive operations necessary for the two tasks and proves that this task dependence can be demonstrated both in relation to, as well as independently of, age-related changes in the control condition.

Another potential factor in our results could be that the older subjects tended to have greater intersubject variability in task performance than the young subgroup. However, this was not reflected in greater variability in utilizing regional cerebral resources. Formal statistical comparison of the variability in rCBF activation for the older and younger cohorts (with Levene's test) revealed no difference in any of the regions in which there were significant correlations between rCBF activation and age ( $P \geq 0.05$ ). Figure 2 graphically demonstrates one example of the absence of increased neurophysiological variability with increasing age.

### ***Task-specific changes in overall activation patterns with age***

The neurofunctional manifestations of the ageing process revealed by the within- and across-task correlational differences suggest that different pathophysiological mechanisms are operational during these two tasks and underlie the age-related cognitive impairments observed with them. In general, where age-related changes occurred during RPM, older subjects exhibited an overall attenuation of the activation/deactivation pattern (Table 2): areas normally activated relative to the control condition by the young subjects (e.g. parahippocampal region, inferior parietal lobule and fusiform gyrus) were not recruited as robustly by the older subjects; areas normally significantly suppressed (e.g. polar frontal cortex and superior temporal lobe) were less suppressed relative to the control. In other words, there was failure to produce a focused neural response by engaging task-appropriate neural activity patterns and inhibiting inappropriate ones; the neural activity patterns during the RPM and the RPMc (and perhaps the cognitive operations employed during them) became more alike in the older cohort. This finding is similar to electrophysiological observations that older subjects do not produce the expected differential activity patterns when challenged with different types of stimuli, such as novel and target items (Friedman and Simpson, 1994). Behavioural observations that older subjects have difficulty with mental flexibility and cognitive focus (Hochanadel and Kaplan, 1994) may reflect these neurobiological underpinnings.

During the WCST, on the other hand, the age-related changes were manifest not only as failure of some normally

activated regions to come on-line relative to the control condition (e.g. dorsolateral prefrontal cortex, inferior parietal lobule and anterior cingulate), but also as recruitment above the control level of regions that typically are not activated, or that are even relatively deactivated, by the young cohort (frontopolar cortex, cuneus and parahippocampal gyrus) as well as suppression relative to control of regions that typically are recruited or unchanged in the younger cohort (Table 1). These results can, like the RPM results, be viewed as failure to focus neurophysiologically by engaging appropriate regional activity and suppressing non-task-related regions, but in this instance may also represent the use of alternative circuitry in an attempt to compensate for the older subjects' inability to bring on-line the appropriate neural network.

### ***Regional task-specific changes in activation with age***

At the level of individual regions, it also appears that many of the identified neurophysiological correlates of ageing were task-specific, depending upon the neural circuitry necessary for the cognitive behaviour. The prefrontal cortex is a case in point. We entered this investigation with the hypothesis that prefrontal functional correlates of ageing might be fluid, varying with the role of the region in performance of the particular task. This proved to be true in one prefrontal area, the left DLPFC (BA 9/45–46). This region was activated by both tasks in the young subgroup, but the effects of age on this activation were significantly different across the WCST and RPM paradigms (Table 3, Figs 1B and 2). DLPFC became *deactivated* with increasing age during the WCST, but remained constantly activated over the age span during RPM.

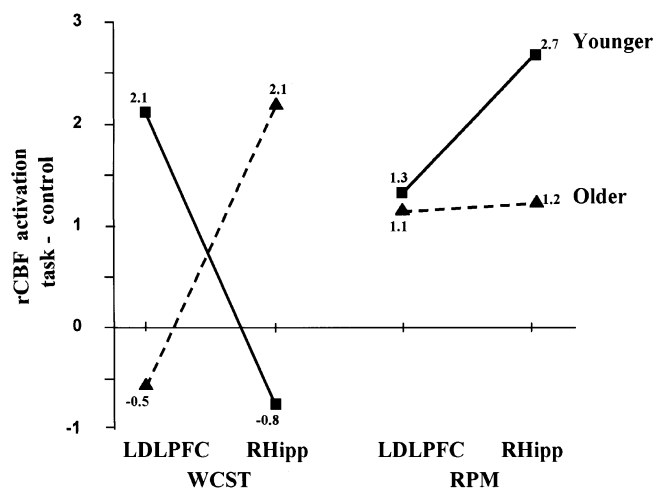
In contrast, the age-activation relationships were similar for both tasks in another prefrontal region, the polar prefrontal cortex (Fig. 1B), which normally is deactivated in both the WCST and RPM paradigms (albeit more so for RPM, Fig. 1A). A positive correlation with age was observed in both tasks (Tables 1 and 2, and top two rows of Fig. 1B). This normally suppressed area actually became activated above baseline in the older subjects during the WCST (Table 1, top right of Fig. 2); during the RPM, there was less functional suppression relative to baseline in the older subjects (Table 2, bottom right of Fig. 2), but they did not activate above the control task level. Thus, despite the fact that the direction and magnitude of the correlations in this area were similar for the two tasks, the underlying pathophysiological mechanism, even here, could still be subtly different: failure to inhibit in RPM appropriately versus actual recruitment of alternative, normally suppressed regions in the WCST (see below).

In more posterior portions of the brain, specifically the inferior parietal lobule (BA 39/40) and inferior temporal cortex (BA 21/37), across-task differences in the age-activation relationship were also demonstrated statistically (see bottom row of Fig. 1B). Interestingly, the directions of the differences were opposite in these two regions and

reflected the directions of the activation patterns in young subjects. In the inferior parietal lobule (BA 39/40), which is activated more robustly during the WCST than RPM in young subjects (Fig. 1A, bottom row, +28 mm), there was significantly greater reduction in activation with age during the WCST. In inferior temporal areas, which are activated more robustly during the RPM than during the WCST in young subjects, there was significantly greater reduction with age during RPM than there was during WCST.

These data clearly demonstrate that the age-related neurofunctional changes in these regions are context-dependent and reflect (i) the differential normal physiological response during the tasks and (ii) the related issue of the importance of the regions for the particular cognitive operations having primacy in the tasks. More specifically, the across-task differences appear to reflect the more circumscribed dependence of the WCST on working memory and prefrontal cortical systems, and of RPM on visuospatial processing systems, computational problem solving and postrolandic regions. This hypothesis is suggested by the observation that, for example, the DLPFC and the inferior parietal lobule showed significantly greater age-related decreases in activation during the WCST than RPM, and these areas have been linked specifically to working memory and to the WCST (Friedman and Goldman-Rakic, 1994; Berman *et al.*, 1995). On the other hand, the inferolateral temporal cortex, which has been related more to visual processing (Haxby *et al.*, 1991) than to working memory *per se*, showed significantly greater age-related decline in function during RPM than WCST, and RPM is more highly dependent on visual processing and more sensitive to damage in this area than in prefrontal cortex (Basso *et al.*, 1973).

Our data also provide evidence that the functional relationship between regions may be altered with ageing. The parahippocampal/hippocampal region is activated consistently in young subjects during RPM, but normally is not activated or is even deactivated during the WCST (Ostrem *et al.*, 1993; Berman *et al.*, 1995; Mattay *et al.*, 1996). We found that the relationship between age and rCBF activation in this region was significantly different across our two task paradigms, with an age-related increase in parahippocampal/hippocampal activation during the WCST and a decrease during the RPM. These findings, together with those in the DLPFC (i.e. decreased activation with age for the WCST and no change during RPM), suggest that alteration of the normal prefrontal–hippocampal functional relationship needed for good performance during the WCST and the RPM (Mattay *et al.*, 1996) is altered in a task-specific manner as age increases. To test this, we performed a *post hoc* three-way ANOVA with one independent measure (group: old versus young) and two repeated measures (task: RPM versus WCST; and region: hippocampal area versus DLPFC). The group  $\times$  task  $\times$  region interaction was highly significant [ $F(1,38) = 13.3$ ,  $P < 0.0008$ , Fig. 3]. Furthermore, during the WCST, a negative correlation between left DLPFC and right parahippocampal/hippocampal gyrus was found in the



**Fig. 3** Task-specific changes in the prefrontal–hippocampal functional interaction with age assessed by three-way analysis of variance (age group  $\times$  task  $\times$  region):  $F(1,38) = 13.3$ ,  $P < 0.0008$ . In the young group (continuous line), activation of the left dorsolateral prefrontal cortex was associated with right hippocampal suppression during the WCST, and with right hippocampal activation during the RPM. In the old group (dashed line), the pattern was largely reversed: reduced activation in the left dorsolateral prefrontal cortex was associated with increased right hippocampal activation during the WCST, whereas during RPM, preserved left dorsolateral prefrontal cortical activation was associated with reduced hippocampal activation. WCST = Wisconsin Card Sorting Test; RPM = Raven's Progressive Matrices; LDLPFC = left dorsolateral prefrontal cortex; RHipp = right hippocampal region.

young subjects ( $r = -0.64$ ;  $P = 0.005$ ), while no such relationship was found in the old subjects ( $r = -0.33$ ;  $P > 0.16$ ). Interestingly, during RPM, there was no correlation between these two regions in the young subjects, but a negative interaction emerged in the older cohort ( $r = -0.48$ ;  $P < 0.05$ ), resembling the one that was operational in the young subjects during the WCST. One interpretation of these results is that some functional relationships that are important for task performance are lost with ageing, while new functional links not typically present may be generated, perhaps in compensation. These results are consistent with previous findings that these two regions are particularly sensitive to the effects of ageing (Grady *et al.*, 1995; Schacter *et al.* 1996; for reviews, see Kemper, 1994; de Leon, 1995). Our data extend those findings by demonstrating that the functional relationship between these two regions and the age-related changes in this relationship are context-dependent and depend upon the neural systems most necessary for the tasks.

To address in a more global sense whether neural networks functional in young subjects are also present in the older subjects, we expanded this *post hoc* exploratory covariance analysis to examine a larger set of potential network nodes. Using the method of Cabeza *et al.* (1997b), we selected from SPM activation analyses a set of voxels for each task activated or deactivated most robustly by the younger subjects. These candidate constituents of the neural networks engaged during

WCST and RPM performance in young subjects were chosen bilaterally from DLPFC, polar prefrontal cortex, anterior cingulate, inferior parietal lobule, parahippocampal/hippocampal region, inferolateral temporal cortex and occipital cortex. From these voxels, we then extracted for each of the two tasks the patterns of regional covariance in the younger subjects, as indicators of interregional functional interactions present during cognitive performance (Horwitz *et al.*, 1991; Cabeza *et al.*, 1997b). The same exploratory analysis for the same voxels was applied to the older group to identify age-related changes in the utilization of the neural networks engaged during our two tasks. During the WCST, anterior–posterior positive covariances were found in the young subjects between the left DLPFC and the left and right inferior parietal lobule ( $P < 0.02$ ), while inverse relationships were found between the left DLPFC and the left polar prefrontal cortex ( $P < 0.05$ ) and, as mentioned above, between the left DLPFC and the right parahippocampal region ( $P = 0.005$ ). However, in the old subjects, there was a dissolution of this covariance pattern, with only the relationship between left DLPFC and right inferior parietal lobule remaining. During the RPM, as expected, young subjects showed a different pattern of functional interactions: the right parahippocampal region positively correlated with the right inferolateral temporal cortex and with the right occipital cortex ( $P < 0.01$ ), as did the right inferolateral temporal cortex with the right inferior parietal lobule ( $P = 0.05$ ), while negative interactions between left polar prefrontal cortex and right inferior parietal lobule and between right polar prefrontal cortex and right lateral prefrontal cortex ( $P < 0.05$ ) were observed. In the older subjects, these interactions disappeared, with the exception of that between the right parahippocampal gyrus and the right inferolateral temporal cortex. Interestingly, in addition to the new inverse relationship between left DLPFC and the right parahippocampal region mentioned above, new positive relationships not seen in the young group arose in the older cohort: right DLPFC activation became correlated with right inferior parietal lobule and with right occipital cortex activation ( $P < 0.05$ ). These *post hoc* analyses suggest that prefrontal–parietal functional interactions within the working memory system and temporal–parietal–hippocampal functional interactions within posterior visuospatial processing systems are altered in older subjects. These results also lend further support to the more general notion that task-specific changes in neural systems occur with ageing.

The context-dependence of these age-related changes and the fact that the functional relationship between regions also changes in a task-specific way, even in the setting of two task paradigms with considerable cognitive overlap, are most consistent with the notions of disconnectivity and systems failure. Disconnectivity, i.e. abnormal functional integration across a distributed network of regions, has been considered as a basis for cognitive dysfunction in a variety of clinical settings (Friston and Frith, 1995). The related term, system failure, refers to functional abnormalities that may become

apparent when cognitive or other demands call for a network of regions to be brought on-line in a coordinated manner; therefore, such abnormalities may, indeed, be context dependent. Whether the prefrontal cortex has a special role in such disconnectivity and system failure, as could be surmised from its central executive function, is a topic for more extensive analysis in future research, perhaps using structural equation modelling.

### Possible mechanisms

There is considerable speculation in the literature about the interpretation and source of age-related neurofunctional changes. At the cognitive level, our finding of context-dependent decreases in neural recruitment in areas important for cognitive performance could represent the primary neurobiological underpinnings of reduced mental capacity. This concept may be particularly relevant in the prefrontal working memory system which is, by definition, of finite capacity (Baddeley, 1992) and which capacity may be limited further with ageing. Our findings of increased activation with age in areas not usually activated could represent secondary changes, i.e. the use of alternative cognitive strategies in the face of those primary limitations (e.g. hippocampal activation during the WCST because of the use of long-term instead of prefrontal short-term working memory mechanisms). Alternatively, these increases could themselves represent primary neurophysiological changes, such as functional inability to suppress activity in regions not important for the cognitive operation (e.g. in polar prefrontal cortex for both tasks), as has been suggested by a number of evoked potential studies (e.g. Friedman and Simpson, 1994; Nielsen-Bohlman and Knight, 1995). This possibility is particularly intriguing given recent suggestions that suppression of rCBF in areas unrelated to the task may be an important mechanism for focusing attention (Roland, 1982; Haxby *et al.*, 1994; Mattay *et al.*, 1996). Hasher and Zacks (1988) argue that inhibition of specific regions in order to suppress processing of irrelevant stimuli is defective in the elderly and is responsible for reduced cognitive performance when the frontal lobe participates in the cognitive operation. Dysfunction of these inhibitory mechanisms would admit extraneous information that would engage the prefrontal system and use neural time, attention and memory resources that should be focused on processing relevant information. The outcome would be a relative reduction of the capacity of the central executive of the working memory system and of the ability of the prefrontal cortex to coordinate and regulate the activity of other regions during cognition, in other words, system failure.

It is instructive to view in light of the capacity-limited nature of working memory the various neurophysiological age effects that occur when DLPFC, itself, is faced with different cognitive demands. In the present study, DLPFC activation is decreased with ageing in the context of a task in which DLPFC is activated in young subjects, working memory plays a primary role and working memory capacity

is exceeded in ageing (i.e. the WCST, top left of Fig. 2). In our other task, RPM, DLPFC is also activated in young subjects, but working memory is not primary to the task and plays a role which may remain within its capacity with ageing; in that context, DLPFC activation remained constant over the age span (bottom left of Fig. 2). In other studies of tasks in which working memory and related prefrontal systems normally play no role and in which DLPFC is not activated in young subjects [visuospatial processing of faces and location (Grady *et al.*, 1994) and memory recall (Cabeza *et al.*, 1997a)], DLPFC activation actually increased with ageing; in that context, working memory and prefrontal systems may have been called upon as a compensatory cognitive strategy in the face of other extra-frontal deficits more primary to the tasks (Grady *et al.*, 1994).

The dopamine system is an attractive candidate in which to search for a common mechanism for these findings because alterations in dopamine receptors, particularly of the D2 type (Volkow *et al.*, 1996a; Wong *et al.*, 1997), and of presynaptic dopamine transporters (van Dyck *et al.*, 1995; Volkow *et al.*, 1996b) have been documented in studies of human ageing and because dopamine plays a special role in prefrontal cortex. In both animals and humans, monoamines modulate cortical signal-to-noise, suppressing spontaneous background neural firing and specifically enhancing cortical neural responses to relevant stimuli (Foote *et al.*, 1975; Sawaguchi, 1987; Arnsten and Goldman-Rakic, 1990; Daniel *et al.*, 1991; Mattay *et al.*, 1996). The context-dependent changes in activation pattern we observed with ageing are well conceptualized as diminished signal-to-noise. In the prefrontal cortex, an optimal range of dopaminergic tone is required for optimal function (Desimone, 1995; Williams and Goldman-Rakic, 1995). Moreover, in a previous study (Mattay *et al.*, 1996), we augmented monoaminergic function with dextroamphetamine while young subjects performed the same two tasks as in the present study and found that during the WCST, activation increased in DLPFC (the 'signal') and decreased in hippocampus (the 'noise'), while exactly the opposite pattern of changes occurred during RPM. Collectively, those task-specific changes in the functional relationship between DLPFC and hippocampus with amphetamine are, in turn, opposite to those that occurred with ageing in the present study (Fig. 3). In a recent study of rodents, D1 receptors were shown to modulate hippocampal–prefrontal cortical circuits (Seamans *et al.*, 1998). Further neuroimaging studies in older subjects with pharmacological manipulation of monoaminergic neurotransmission may clarify the role of this system in cognitive deficits in ageing.

## Conclusions

We used two tasks with considerable cognitive overlap, but some important differences in cognitive features and neural substrate. Those differences were reflected in differential neurophysiological manifestations of ageing during

performance of the two tasks. The context dependency of the neurofunctional findings is most consistent with the notions of system failure and disconnectivity, but prefrontal impairment may play a special role. The older subjects' impaired neurophysiological focus—their inability to bring the appropriate systems on-line while suppressing others—appears to underly their impaired performance on both tasks. In this study, we took advantage of our cohort's even age distribution to search for linear relationships between age and rCBF activation. It is possible that non-linear analyses would yield additional information. New statistical approaches, such as that employed in the present study, may help to explore further the important role that altered interregional functional connectivity appears to have in the decline of some higher cognitive functions with age (Wickelgren, 1996). The present study has the limitations of any cross-sectional investigation on the effects of normal ageing. Within-subject longitudinal studies are likely to have increased sensitivity to age-related neurofunctional changes. Finally, this work emphasizes that tasks accessing relevant neural systems must be used to measure neurofunctional changes with ageing and that those changes must be interpreted in light of the role of the particular neural structure in the cognitive operation being studied.

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