# Regional cerebral blood flow as assessed by principal component analysis and $^{99m}$Tc-HMPAO SPET in healthy subjects at rest: normal distribution and effect of age and gender

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**Abstract.** The increasing implementation of standardisation techniques in brain research and clinical diagnosis has highlighted the importance of reliable baseline data from normal control subjects for inter-subject analysis. In this context, knowledge of the regional cerebral blood flow (rCBF) distribution in normal ageing is a factor of the utmost importance. In the present study, rCBF was investigated in 50 healthy volunteers (25 men, 25 women), aged 31–78 years, who were examined at rest by means of single-photon emission tomography (SPET) using technetium-99m *d,l*-hexamethylpropylene amine oxime (HMPAO). After normalising the CBF data, 27 left and 27 right volumes of interest (VOIs) were selected and automatically outlined by standardisation software (computerised brain atlas). The heavy load of flow data thus obtained was reduced in number and grouped in factors by means of principal component analysis (PCA). PCA extracted 12 components explaining 81% of the variance and including the vast majority of cortical and subcortical regions. Analysis of variance and regression analyses were performed for rCBF, age and gender before PCA was applied and subsequently for each single extracted factor. There was a significantly higher CBF on the right side than on the left side ($P$<0.001). In the overall analysis, a significant decrease was found in CBF ($P$=0.05) with increasing age, and this decrease was particularly evident in the left hemisphere ($P$=0.006). When gender was specifically analysed, CBF was found to decrease significantly with increasing age in females ($P$=0.037) but not in males. Furthermore, a significant decrease in rCBF with increasing age was found in the brain vertex ($P$=0.05), left frontotemporal cortex ($P$=0.012) and temporocingulate cortex ($P$=0.003). By contrast, relative rCBF in central structures increased with age ($P$=0.001). The ability of standardisation software and PCA to identify functionally connected brain regions might contribute to a better understanding of the relationships between rCBF at rest, anatomically defined brain structures, ageing and gender.

*Keywords:* SPET – rCBF – Normal – Distribution – Principal component analysis

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## Introduction

The importance of brain imaging in the assessment of cerebrovascular and neurodegenerative disorders is steadily increasing. Different techniques for functional and anatomical examination are being clinically implemented in neurology and psychiatry to improve the sensitivity and accuracy in the diagnosis of various diseases. In addition, the increasing life expectancy in the Western world is adding to the social importance and the economic impact of age-related neurodegenerative disorders. In this scenario, and for the planning of future treatment protocols, it is becoming ever more important

to identify and characterise the "natural" changes in regional cerebral blood flow (rCBF) distribution that occur during normal ageing.

Brain volume standardisation techniques are nowadays often implemented to improve the diagnostic accuracy in cerebral disorders [1, 2, 3, 4, 5]. They require a number of control cases to be matched to clinical studies, allowing for evaluation of a patient scan by comparison of the results with a reference database. Knowledge of the normal distribution of the radiopharmaceutical in the brain is mandatory when estimating pathological alterations in rCBF. Furthermore, recent studies have claimed that there is a need to perform explicit measurements of covariance structures at baseline in order to determine functionally coupled brain regions [6, 7].

The need to define normality of the nervous system, even in the elderly, and the importance of the reliability of control groups in functional imaging have recently been underscored. On this basis, stricter selection of normal volunteers for inclusion in studies has been proposed. Control populations need to be chosen according to features defining normal ageing of the nervous system [8] and should be recruited exclusively for the purpose [9].

In recent years, a number of studies have analysed the changes in rCBF distribution that occur with increasing age. A preferential right-sided CBF distribution has been reported [10, 11, 12, 13]. Left/right asymmetry has been recognised to increase with age [14, 15], and age has been found to affect both global [11, 12, 16] and regional [15, 17, 18, 19, 20, 21] CBF. In contrast, however, Yamaguchi et al. [22] did not find any age-dependent decrease in rCBF.

From previous studies it appears that the assessment of rCBF varies depending on the radiopharmaceutical used, the mean age of the investigated groups and the methodology employed. In addition, rCBF analysis has been carried out with different manual, semi-automatic and automatic methods for outlining the regions of interest, and the choice of method has also been shown to affect the results [23].

One of the problems faced when attempting to properly map the CBF distribution is the large variety of regions under study and hence the large number of anatomically defined functional variables obtained. The issue of how to deal with this statistical problem is still under discussion [24].

In attempts to overcome this difficulty, some authors have employed principal component analysis (PCA), where the number of independent variables across subjects can be reduced to permit more detailed investigations of the "functional connectivity" [25, 26, 27, 28, 29]. The resulting components, or factors, are not assessed in advance but are extracted as a result of the statistical procedure.

The aim of the present study was to investigate the rCBF distribution and the blood flow correlation across brain regions in a group of strictly selected healthy individuals at rest by means of PCA. This was accomplished by using advanced anatomical standardisation software and technetium-99m *d,l*-hexamethylpropylene amine oxime (HMPAO) single-photon emission tomography (SPET).

## Materials and methods

### Subjects

Fifty subjects were included in this investigation. These volunteers were recruited from among the friends and spouses of stroke patients hospitalised at the Department of Neurology, Karolinska Hospital.

To be accepted as a participant in the study, subjects had to be judged as physically and mentally healthy according to their own assessment and that of the examining physician. Only subjects receiving no medication and with no history of physical or mental illness, alcohol or drug abuse were selected for further examination. Exclusion criteria included previous brain trauma, cerebrovascular disorder, hypertension, diabetes, epilepsy, psychiatric disorders, allergy or any other systemic disease or malignancy and chronic drug treatment.

Each subject was given a physical examination including evaluation on two different neurological rating scales, i.e. the NIH Stroke Scale [30] and the Scandinavian Stroke Scale (SSS) [31]. A psychiatric interview was also performed and included rating on a subscale of the Comprehensive Psychopathological Rating Scale [32], the Montgomery-Åsberg Depression Rating Scale (MADRS) [33] and Mini Mental State Examination (MMSE) [34, 35]. In addition, smoking habits and dexterity were recorded for each individual. Routine laboratory samples, including haemoglobin (Hb) and haematocrit (Ht), were taken on the same day as the physical examination and analysed for blood characteristics and liver and kidney functions. All subjects were asked not to take any salicylates for at least 1 week prior to blood sampling and participation in the SPET investigation and they were also asked to abstain from coffee, tea and nicotine for 2 h prior to the SPET examination.

Blood pressure was recorded in supine position at the time of physical examination and after 30 min of rest prior to the injection of $^{99m}$Tc-HMPAO.

This group of subjects was selected to specifically serve as a normal healthy control group for SPET analysis and none of the subjects underwent any other nuclear medicine examination for diagnostic purposes. All subjects received both oral and written information about the study from the responsible physician and gave their written informed consent. The study was approved by the ethical committee and the radiation safety committee of Karolinska Hospital.

### Methods

*Radiopharmaceutical and SPET examination.* After 30 min rest in a tranquil place with dimmed light, 1,000 MBq (27.0 mCi) of $^{99m}$Tc-HMPAO (Ceretec, Amersham International plc, Little Chalfont, UK) was injected intravenously within 15 min after reconstitution. The radiopharmaceutical was prepared strictly according to the manufacturer's instructions. SPET brain imaging was performed using a triple-headed gamma camera (TRIAD XLT 20,

Trionix Research Laboratory Inc., Twinsburg, Ohio, USA) equipped with low-energy high-resolution (LEHR) collimators. The projection data were acquired for 15 s per projection at 90 equal angles of a complete revolution (0–360°).

Before reconstruction, the projection data were pre-processed using a 2D Hamming filter with a cut-off frequency of 2.25 cycles/cm. Sectional images were reconstructed by filtered back-projection using a Ramp filter with a cut-off frequency of 0.6 cycles/cm. During pre-processing, correction for attenuation was performed using the uniform Chang method [36]. No scatter correction was applied. Both acquisition and reconstruction were performed in 128×128 matrices with a pixel size of 2.22×2.22 $mm^2$.

*Computerised brain atlas.* The computerised brain atlas (CBA) is a software tool for analysis of neuroimaging data [37, 38]. It is based on a detailed 3D atlas derived from a cryosectioned brain. In this study the fully automatic method was systematically implemented [39].

All image sets were spatially normalised into the stereotactic space of the atlas by using the global polynomial transformation implemented in the CBA software [40]. It consists of translations, rotations and linear scalings along and around each of the three image axes. It also contains 18 non-linear shape-deforming parameters, which makes it possible to individualise the shape of the brain. In order to achieve optimal fitting of the atlas to the SPET data pool, eight of the possible 18 polynomial transformation parameters acting on the three axes were used. This choice was originally based on the visual evaluation of the best fully automatic fitting obtained. A cross-correlation cost function was used as a similarity measure for registration and Powell's method [41] was used for the optimisation. After the registration all images were resliced into an image matrix of 128×128×48 with voxel dimensions of 2.22×2.22×2.81 mm.

For evaluation and statistical analysis of the reformatted data sets, 27 volumes of interest (VOIs), bilaterally, were selected; these VOIs corresponded to Brodmann areas (B) in prefrontal (B9, B10, B46), frontal (B4, B6, B8, B44, B45), parietal (B1–3, B5, B7, B39, B40) temporal (B21, B37, B38), auditory (B22, B41, B42, B52, these four regions being assessed as a single VOI), cingulate (B24, B31, B32) and occipital (B17, B18, B19) cortex as well as putamen, nucleus caudatus, thalamus and hippocampus. Cerebellar regions were excluded owing to the poor fitting of the atlas to this particular region. In order to obtain standardised relative flow data, a correction factor was computed by averaging all brain voxels and setting the global brain average to a predefined value. However, in order to prevent overestimation of uptake in subjects in whom large regions of pathological low flow might be present, histogram analysis was used to exclude voxels with low uptake values from the normalisation process. A fixed counts/voxel threshold was selected to reject 87% of all voxels in each set of 3D images. In this way only the remaining 13% of voxels with the highest flow were used for normalisation. The choice of the upper 13% of all voxels was made from the analysis of the volume involved in normal rCBF scans. It allowed the inclusion of almost all of the voxels containing grey matter in the normalisation process.

Since in this investigation the material under study was from strictly controlled normal subjects, free of any neurological, neurodegenerative or psychiatric disorders, our main concern was the best means of evaluation of the previously reported physiological rCBF decrease due to normal ageing. The above-described normalisation method, which is particularly suited to the detection of decreases in rCBF, was chosen on this basis.

The normalised value (the average count rate in the upper 13% of all voxels) was set to 50 "uptake units". All rCBF values of this work were related to this standard value.

*Data analysis.* After adaptation and definition of VOIs using the CBA software, the VOI data of all subjects were exported to a statistical package (SYSTAT 9) for subsequent statistical analysis of $^{99m}$Tc-HMPAO uptake in all 54 predefined brain regions. PCA and varimax rotation were performed in order to assess inter-relationships among regions. PCA involves a mathematical procedure that transforms consecutively a number of (possibly) correlated variables into a (smaller) number of non-correlated factors called principal components. The first principal component accounts for the highest percentage of the global variability between the data and each succeeding component accounts for the remaining variability in a descending scale. PCA provides a unique solution, so that the original data can be reconstructed from the results.

The number of factors to be extracted was determined after examining both the eigenvalue and the scree plot. In order to obtain a meaningful reduction in the large number of variables, an eigenvalue greater than 1.2 was selected. Variables with a factor loading greater than 0.5 were extracted for each factor.

Analysis of variance (ANOVA) was used to test the statistical significance of flow data considering age and gender as independent variables. Before implementing PCA, regression analyses and *t* test were performed, calculating the mean of the sum of the rCBF intensities in all VOIs ($n$=54) of each subject under study. These mean values were used to investigate the effect of age, gender, Hb and Ht on CBF. When the two hemispheres were studied separately, a mean value representing the mean of the sums of the rCBF intensities in all VOIs in the left or the right hemisphere was calculated.

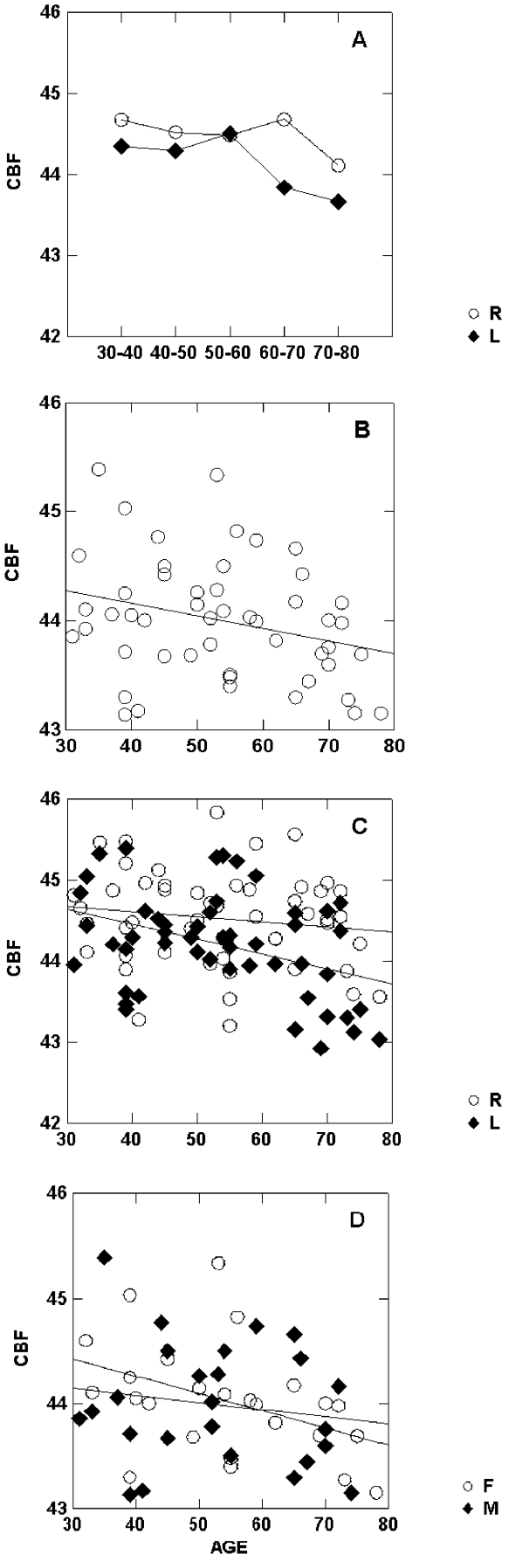
## Results

The mean age of the 50 healthy control subjects was 53±13 (range 31–78 years). The gender distribution was equal, with 25 females (mean age±SD 54±13 years) and 25 males (mean age±SD 52±13 years). Eight subjects were users of nicotine and two subjects were left-handed.

All subjects scored 0 points on the NIH scale, 58 points on the SSS scale and 0 points on the MADRS scale. The mean value (±SD) on the MMSE was 29.3±0.7 points (full score 30 points). Taken together, these ratings indicate the absence of any significant neurological and/or psychiatric disturbances. None of the subjects had high blood pressure at either of the two measurements, and no correlation was found between blood pressure and rCBF in any of the investigated regions.

Significant differences were found in Hb and Ht values between males and females (*t* test=4.926, $df$=47, $P$<0.001; *t* test=3.548, $df$=48, $P$=0.001, respectively) but these two variables were not found to affect CBF.

A significant asymmetry was found, with higher CBF values in the right hemisphere than in the left hemisphere [44.52 vs 44.20, $F(1,40)=19.362$; $P$=0.001]. When the subjects were divided according to decade of



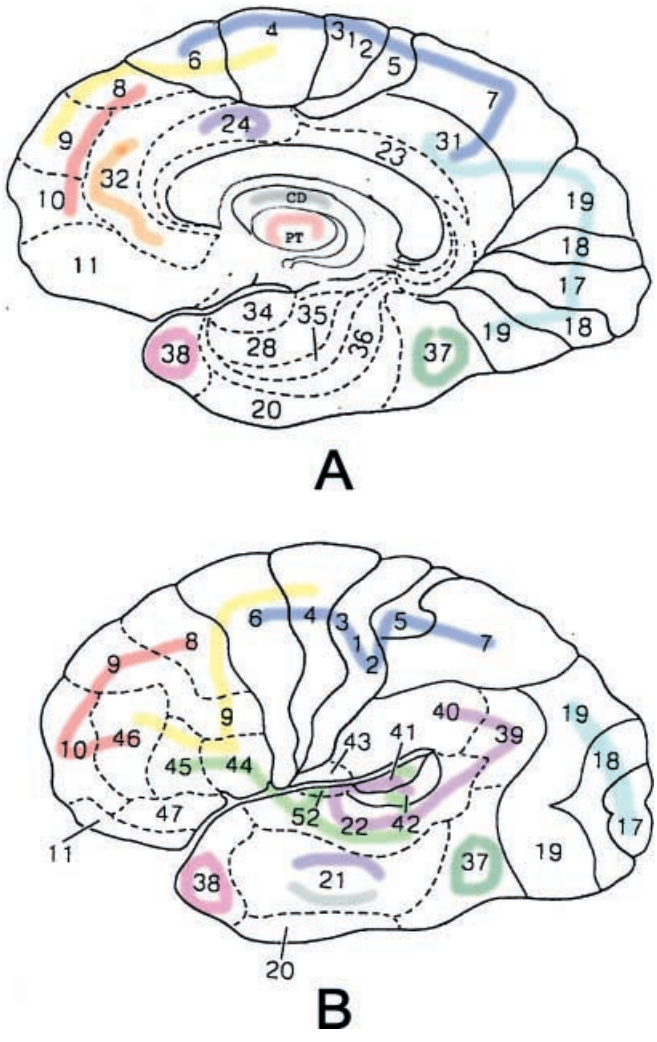




**Fig. 2.** Medial (**A**) and lateral (**B**) brain representation of the factorial grouping of VOIs following PCA. Brodmann areas (depicted according to Brodmann numeration) grouped in the same factors are linked by the same colour. The lateral representation is a virtual fusion of the left and right hemispheres

age, the largest difference between right and left hemispheres was found in the group between 60 and 70 years old [$F(4,40)=4.087$; $P=0.007$; Fig. 1A].

A significant overall effect of age on CBF was found by regression analysis [$F(1,48)=4.079$; $P=0.05$, Fig. 1B]. While no effect of age on the right hemisphere CBF was found, its effect on the left hemisphere CBF was significant

◀ **Fig. 1A–D.** Overall relationships between CBF and age in 50 normal healthy controls. **A** Left and right hemisphere overall CBF values when subjects were grouped by decades of age. **B–D** Regression analysis between overall CBF in each subject and age (**B**), between left and right hemisphere CBF in each subject and age (**C**) and between overall CBF in males ($n=25$) and in females ($n=25$) and age (**D**). Regressions between age and overall CBF, right hemisphere CBF and overall CBF in females reached the level of significance ($P=0.05$). *R*, Right; *L*, left; *M*, males; *F*, females. Mean CBF values are normalised to 50

**Table 1.** Factorial grouping of VOIs following principal component analysis

| Factors | Anatomical description | Grouped VOIs (B) | Mean | SD | rCBF* age | | Percent of total variance explained |
|---|---|---|---|---|---|---|---|
| | | | | | *F*(1,48) | *P* | |
| 1 | BV | B4L, B5R, B5L, B6L, B7R, B7L, B31L, B1–3R, B1–3L | 46.0 | 1.3 | 4.14 | 0.048 | 16.93 |
| 2 | LAF | B8L, B9L, B10L, B46L | 44.3 | 1.2 | | | 13.97 |
| 3 | RTP | AUDR, B39R, B40R | 42.7 | 1.1 | | | 9.37 |
| 4 | LFT | AUDL, B44L, B45L, HPL | 43.6 | 1.4 | 6.75 | 0.012 | 7.53 |
| 5 | O | B17R, B17L, B18R, B18L, B19L, B31R | 44.7 | 1.5 | | | 6.50 |
| 6 | RF | B4R, B6R, B8R, B9R, B44R, B45R, B46R | 45.3 | 1.1 | | | 6.11 |
| 7 | CS | PTR, PTL, THR, THL | 49.7 | 1.5 | 12.17 | 0.001 | 4.98 |
| 8 | TC | B21R, B24R, B24L | 41.7 | 1.5 | 10.09 | 0.003 | 3.98 |
| 9 | AT | B38R, B38L | 37.5 | 1.7 | | | 3.59 |
| 10 | TCa | B21L, CDR, CDL | 41.3 | 1.4 | | | 2.91 |
| 11 | PT | B37R, B37L | 42.5 | 1.7 | | | 2.79 |
| 12 | AC | B32R, B32L | 48.8 | 1.3 | | | 2.32 |

Mean CBF values are normalised to 50
BV, Brain vertex; LAF, left anterofrontal cortex; RTP, right temporoparietal cortex; LFT, left frontotemporal cortex; O, occipital cortex; RF, right frontal cortex; CS, central structures; TC, temporocingulate regions; AT, anterior temporal cortex; TCa, temporocaudatal; PT, posterior temporal cortex; AC, anterior cingulate cortex; VOI, volume of interest; B, Brodmann areas; L, left; R, right

[$F(1,48)=8.447$; $P=0.006$, Fig. 1C]. When gender was taken into account, regression analysis showed that ageing had no effect on CBF in males but did have a significant effect on CBF in females [$F(1,23)=4.908$, $P=0.037$, Fig. 1D].

PCA, performed on the 27 left and 27 right VOIs, resulted in 12 factors of descending significance (Table 1, Fig. 2). These orthogonal and uncorrelated factors explained 81% of the total data variance for the sample.

There was a significant difference between factors [$F(11,440)=278.2$; $P<0.001$]. Most of the factors grouped either left and right corresponding VOIs (anterior or temporal, posterior temporal, anterior cingulate) or clusters of adjacent left or right regions (anterior left frontal, right frontal). Within each factor, all possible correlations ($n=102$) between the variables, except two, were found to be positive.

The left and right superior somatosensory parietal (B1-3, B5, B7), left premotor (B6), motor (B4) and posterior cingulate (B31) cortex were grouped together (brain vertex). The left and right thalamus and putamen formed a separate group (central structures), as did most of the VOIs of the occipital cortex. A higher rCBF was found in the factors related to central structures and the anterior cingulate cortex. The lowest rCBF values were obtained in factors grouping the anterior temporal cortex and nucleus caudatus (Table 1).

There was a significant decrease in rCBF with increasing age in the brain vertex, left frontotemporal cortex and temporocingulate cortex (Fig. 3A–C). On the other hand, rCBF in central structures increased with age (Fig. 3D).

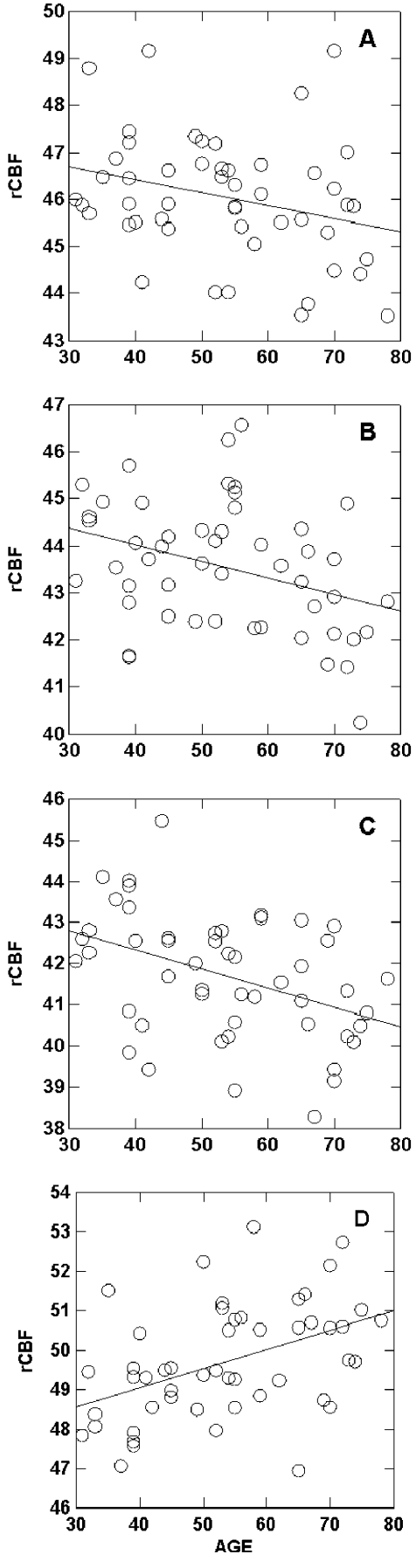
When gender was reconsidered, the only significant difference was a reduced flow in males in the posterior temporal cortex [43.07 vs 41.98; $F(1,48)=5.376$, $P=0.025$].

## Discussion

In brain research, most studies have been performed by analysing a small selected number of regions obtained using manually defined regions of interest. However, this approach requires a predetermined working hypothesis and the selection of regions has to be based on the accepted data in the literature. In this study, complete and accurate mapping of blood flow in the cerebral cortex and in the most important central structures was undertaken. Investigating all or most of the available regions outlined by the CBA (VOIs) would have resulted in a statistical analysis of data from a very large number of cerebral regions.

Implementing an algorithm for analysis of covariance, statistical parametric mapping enables identification of clusters of voxels showing significant differences between images acquired under different conditions and suggesting regional brain specialisation. Clark et al. [42] pointed out that these findings might be a consequence of regional coupling rather than regional specialisation. They therefore proposed the use of variance partitioning using PCA rather than null hypothesis testing approaches in order to separate the signal variance due to functional activation from that due to methodological or anatomical factors. In PCA each component is orthogonal and functionally not correlated to the remaining ones. PCA sorts subject-region interaction and guarantees that regional coupling has been accounted for.

The modifications induced in brain rCBF by cortical activation or by a pathological state alter the variance-covariance of the measurement and hence functional connectivity. However, the functional connectivity in a




human brain is very much dependent on the state of the brain at the time of measurement [6]. It will vary, as compared with the resting state, when performing an activation task. Heterogeneous covariance brain structures reflecting functional connectivity have been found to underlie baseline activation studies [6, 29] and to be responsible for significant inter-subject variability [43]. Such interaction terms due to methodology-subject-region interactions cannot be neglected [7].

Factor analysis using PCA has seldom been used as a tool for statistical analysis in medical imaging [6, 29, 44, 45]. Nevertheless, it has been applied in previous SPET studies in order to reduce the number of variables before performing the statistical analysis [46, 47, 48, 49]. However, in these investigations none of the different brain regions at rest were grouped by independent components.

In our study, PCA reduced the number of initial variables in 50 normal controls from 54 VOIs into 12 factors representing 81% of the total data variance. The main finding of the study was the rather good consistency between the factors identified by PCA and neuro-anatomical and functional connections. These results were all obtained under the resting state in a quiet, dimly lit room. This strong rCBF correlation within the same factors may result from methodological, subjective or anatomically defined functional parameters.

The first component, factor 1, grouped left and right regions located in the brain vertex. Since we analysed the SPET results by applying a single four-point ellipse and Chang attenuation correction [36], this finding could be correlated to the overestimation of rCBF in these regions [50].

Other factors grouped left or right clusters of Brodmann areas. Factor 6, for example, included right motor, premotor and association dorsolateral and prefrontal cortex while factor 2 grouped left prefrontal and frontal cortex. Corresponding left and right Brodmann areas or anatomically defined structures (i.e. temporal and anterior cingulate cortex or central structures) were coupled in each of the factors 7–12. A similar pattern of blood supply at rest between corresponding left and right regions or strong anatomically defined functional correlations between adjacent regions might account for the rCBF coupling between these areas. This latter factor may also explain the grouping in factor 3, in which the right auditory cortex (primary and association) including B22 is grouped together with the right parieto-occipito-temporal junction area, including the angular gyrus (B39). These two Brodmann areas are components of the regions necessary for the comprehension of language.

◀ **Fig. 3.** Regression analyses between rCBF and age in the brain vertex (**A**), left frontotemporal cortex (**B**), temporocingulate regions (**C**) and central structures (**D**). Mean CBF values are normalised to 50. All these regressions reached the level of significance ($P$=0.05)

The left auditory cortex was coupled in factor 4 with the "motor speech memory" area (Broca's area, B44 and B45). This connection was previously observed when studying the glucose metabolic rate with PET during an auditory task [51]. This is a well-known connection in the dominant hemisphere, in which Broca's area receives input from Wernicke's area via the arcuate fasciculus.

The primary and secondary visual cortex, which share obvious strong neural connections, were grouped in factor 5.

Owing to the statistical criteria on which PCA is based, all correlations between variables within each factor were significant. It is interesting to note that 100 out of 102 such correlations were positive, indicating a common behaviour of rCBF at rest in regions anatomically and functionally correlated.

Another important finding was the decreased rCBF in clusters of VOIs belonging to the brain vertex, left frontotemporal and temporocingulate cortex and the parallel increase in the thalamus and putamen with increasing age. This supports the findings of a number of previous studies in which the rCBF in frontal cortex [10, 12, 15, 17, 18, 20, 21, 52, 53] and in cingulate cortex [15, 17, 18, 20, 21, 53] was found to decrease with age. Even though our healthy controls were carefully screened for clinical symptoms, an underlying asymptomatic brain disease cannot be a priori ruled out. However, these findings are very likely related to normal aging per se, in which some regions of the brain show a selective decrease in rCBF. This may be a consequence of reduced blood supply and/or decreased metabolic needs with increasing age. In a recent study, Claus et al. [19] found an age-related reduction in rCBF in parietotemporal cortex but not in frontal cortex. The old age of the groups under study could provide a possible explanation for this finding. On the other hand, Meltzer et al. [54], in a PET/MRI study, reported that after correction for cerebral atrophy, CBF did not decline with age. Owing to the lack of neuro-anatomical measurements in this study, we did not apply any correction for cortical atrophy. However, the presence of a certain degree of cortical atrophy in older subjects may have some effect on the rCBF values and their reduction with age.

The finding of a significant increase in flow with age, as assessed by factor 7, grouping thalamus and putamen, is consistent with a previous report indicating a relative increase in rCBF with age in central structures [16]. In this respect the implemented method could have played an important role. $^{99m}$Tc-HMPAO SPET gives relative results where each value represents a proportion of rCBF in the region used for normalisation. Assuming that the cortical blood flow as a whole, including the white matter part of the analysed VOIs, decreases with age, the relative rCBF in central structures, i.e. thalamus and putamen, which are high-flow grey matter regions, will be proportionally increased.

Anterior temporal pole and temporocaudatal regions were found to have a lower relative rCBF distribution. The finding of a low rCBF for the temporal pole was also reported by Leenders et al. [55]. The relatively low rCBF in these regions could be partially due to their anatomical location. In fact the temporal pole and the nucleus caudatus are surrounded by no-flow regions (cerebrospinal fluid and cerebral ventricles). Furthermore, the partial volume effect phenomenon, which particularly affects SPET data owing to the low spatial resolution of this imaging technique, may have caused an underestimation of the detected rCBF.

Higher rCBF was found in central structures and the anterior cingulate cortex. A high relative rCBF distribution in both central structures [13, 22, 56] and the anterior cingulate cortex [22, 57] has previously been reported by others. However, in a SPET ECD study, Tanaka et al. [21] found a high relative rCBF in thalamus and occipital cortex with a concomitant low rCBF in anterior cingulate cortex. This latter finding was also reported by Koyama et al. [56] in an HMPAO study. These discrepancies could be a result of a different distribution of ECD and HMPAO in brain or to differences in the methodology employed to define the regions or volumes of interest.

A flow asymmetry between hemispheres of the brain, with higher flow on the right side, has previously been reported in other rCBF studies [10, 12, 13, 53], and was confirmed by our data. The significant difference in rCBF in the posterior temporal region that was observed between males and females was also in accordance with a previous finding reported by Jones et al. [28]. However, to our knowledge the unexpected finding of a significant decrease in CBF with age in females but not in males has not been previously reported and requires further investigation in a larger group of individuals.

The results reported here show that with increasing age there is a decrease in rCBF in frontoparietal regions and a parallel increase in central structures. In this respect PCA can be considered a valuable tool for the analysis of brain physiology. In this study, regions sharing very close anatomically defined functional relationships were grouped by the same factors, suggesting a certain degree of functional connectivity of the human brain at rest.

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