Partial Correlation Coefficients Approximate the Real Intrasubject Correlation Pattern in the Analysis of Interregional Relations of Cerebral Metabolic Activity

Barry Horwitz and Stanley I. Rapoport

Laboratory of Neurosciences, National Institute on Aging, National Institutes of Health, Bethesda, Maryland

Correlation coefficients between pairs of regional glucose metabolic rates have been used to assess patterns of functional associations among brain regions in humans and animals. Partial correlation coefficients (partialing out the global metabolic rate) or correlations between reference ratios (regional to global metabolic rate) have been used to remove the distorting influence of systematic intersubject differences in glucose utilization. Suggesting that partial correlations may not preserve the true (but unknown) intrasubject correlation structure within the brain, others have used a theoretical example to show how an artifactually large negative partial correlation coefficient might arise. Here, we show that such an example is highly unlikely when applied to resting cerebral metabolism, and can be identified in experimental data by testing for a bimodal distribution of partial correlation values. We then show that partial correlations or reference ratio correlations of experimental resting metabolic rates give values which closely approximate the intrasubject correlation coefficients.

J Nucl Med 29:392–399, 1988

Because the brain is organized into frequently overlapping neuroanatomic and functional systems (*2*), several efforts have been mounted to determine functional interactions among brain regions in specific groups of subjects under given experimental conditions. Generally, the functional interactions have been evaluated by correlating, across subjects, regional values of a measured quantity related to local neuronal activity. Early efforts used macroscopic electrical measurements of brain activity (e.g., obtained from electroencephalographic or evoked potential studies) in the correlation analysis (*3–5*). More recently, we and others correlated regional cerebral metabolic rates for glucose (rCMRglc) (*6–8*), obtained in humans by positron emission tomography (PET), and in animals by quantitative autoradiography (*9*).

Changes in glucose uptake have been shown in human and animal studies to be related to changes in cerebral functional activity (*10–12*). By correlating rCMRglc between pairs of regions, a correlation matrix is obtained that can display the pattern of functional associations for the entire brain (*6–9*). Different patterns have been found between healthy young and elderly men at rest (*13*), between demented patients and healthy controls (*14,15*), between subjects given pain stimulation and controls (*8*), and between split-brain and sham-operated rats at rest (*16*).

A complication of the correlation matrix method in metabolic studies is that intersubject differences in rCMRglc often are larger than intrasubject differences. This causes essentially all pair-wise correlation coefficients to have large values (*6*). Two procedures have been used to overcome this difficulty. One uses correlations between reference ratios (the ratio of rCMRglc to some measure of global cerebral metabolism) (*7,8*). The other uses partial correlation coefficients, in which the controlled parameter is some measure of global cerebral metabolism (which we take to be the hemispheric average cerebral metabolic rate for glucose, CMRglc) (*6,9*). The matrix of correlations is then put into a form to be examined by retaining only those correlations that meet a specified criterion of statistical acceptability. For the data sets treated by our laboratory

Received Feb. 17, 1987; revision accepted Aug. 10, 1987.

For reprints contact: Barry Horwitz, MD, Lab. Neurosci., NIA/NIH, Bldg. 10, Rm. 6C-103, Bethesda, MD 20892.

(*6,9,13,14*), there is little difference between the correlation matrices obtained using either the reference ratio or partial correlation procedure (Horwitz and Soncrant: unpublished observations).

Recently, the use of partial correlation coefficients has been criticized by Ford (*1*). Ford's major objection was that partial correlation coefficients may not reflect, on occasion, the underlying intrasubject correlation pattern. He used a theoretical example to show how an artifactual, statistically significant, negative partial correlation coefficient might arise, and concluded that, because artifacts can occur, "any results produced using the partial correlation approach should be treated with extreme caution" (1). He did not address the likelihood of this event. Ford also suggested that using reference ratios to obtain a correlation matrix may be as problematic as using the partial correlation method.

In this paper, we show that Ford's objection to the use of partial correlation coefficients (or to the use of correlations of reference ratios) does not apply to real resting brain metabolic rates. We show that a correlation matrix, obtained using actual values of rCMRglc in 20 healthy men whose global metabolic rates are approximately equal (so that CMRglc need not be partialed out), has the same structure as the partial correlation matrix (and, as the reference ratio correlation matrix) derived from measurements in 60 healthy men, of which the 20 are a subset. We also explain why an artifactual negative partial correlation coefficient arises in Ford's example, show that his example represents a highly unlikely biologic condition, and demonstrate how this condition, if present, can be identified.

METHODS

Values for rCMRglc used in this study were obtained from PET scans done as part of the Laboratory of Neurosciences' examination of aging in healthy men (*17–19*). Sixty healthy male volunteers between the ages of 20 and 83 yr (mean ± s.d.: 48 ± 18 yr) were scanned with an ECAT II positron emission tomograph (Ortec; Life Sciences, Oak Ridge, TN) in the medium resolution mode (full width at half-maximum = 1.7 cm in the image and axial planes) using 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG). Criteria for subject inclusion in the study have been detailed elsewhere (*17–19*). All subjects fulfilled stringent medical, neurologic, and psychiatric criteria on examination. Data from 40 of these subjects were used in the correlation matrix analysis of Horwitz et al. (*6*).

rCMRglc (mg/100 g/min) was measured using the operational equation and constants of Huang et al. (*20*). All subjects lay supine but awake, in a dark, quiet room, with their eyes covered and their ears plugged with cotton during the 45-min time interval following the injection of [^{18}F]FDG. Up to seven serial PET slices, 1.4 cm apart, were obtained 5 to 100 mm above and parallel to the externally defined inferior orbitomeatal (IOM) line.

Details of how the PET data were analyzed also have been presented elsewhere (*6,13,17,18*). In brief, the brain was divided into 59 regions of interest (ROI), which are listed in Table 1 (see also Fig. 1) of Horwitz et al. (*6*), and rCMRglc for each region in the 60 subjects was determined. A measure of global metabolism, the hemispheric average of glucose utilization, CMRglc, also was determined. For the 60 subjects, CMRglc ranged between 1.97 and 7.87 mg/100 g/min, with a mean (±s.d.) of 4.88 (±1.10) mg/100 g/min.

RESULTS

Objection to Using Partial Correlation Coefficients

We first summarize Ford's critique (*1*) of the use of partial correlation coefficients. The following will explain how an artifactual statistically significant partial correlation coefficient arises in Ford's example, and why this situation is unlikely to occur in a real brain.

The statistical model for the data used by Ford (*1*) is

$$X_{rs} = \mu_s + p_r + \epsilon_{rs}, \quad (1)$$

where X_{rs} denotes the measured rCMRglc in the sth ROI of subject r(r = 1, 2, . . . , R; s = 1, 2, . . . , S), μ_s represents the mean metabolic rate in region s, p_r is the "subject effect" for the rth subject, and ϵ_{rs} is the random component representing the variability in metabolic rate within a subject.

The intersubject correlation between regions i and j is given by

$$\rho_{ij} = \frac{\sigma_{ij}}{\sqrt{\sigma_{ii}\sigma_{jj}}}, \quad (2)$$

where σ_{ij} is the ijth matrix element of the S × S intersubject covariance matrix. For the model of Eq. (1)

$$\sigma_{ij} = \sigma^2 + \tau_{ij}, \quad (3)$$

where τ_{ij} is the intrasubject covariance between regions i and j, and σ^2 is the (unknown) between-subject variance (*1*). The quantity of interest, what Ford (*1*) calls the intrasubject correlation, is given by

$$\theta_{ij} = \frac{\tau_{ij}}{\sqrt{\tau_{ii}\tau_{jj}}}. \quad (4)$$

The assumption of the correlation approach is that τ_{ij} is a measure of the functional coupling between regions i and j. Combining Eqs. (2)–(4) gives

$$\rho_{ij} = \frac{\sigma^2 + \tau_{ij}}{\sqrt{(\sigma^2 + \tau_{ii})(\sigma^2 + \tau_{jj})}}. \quad (5)$$

If there were no between-subject variance (i.e., $\sigma^2 = 0$), the correlation coefficient of the absolute metabolic values would represent the intrasubject correlation (i.e., $\rho_{ij} = \theta_{ij}$). For the additive model of the data, given by Eq. (1), the source of the between-subject variance is the term p_r, the "subject effect". When the between-subject variance is large (i.e., $\sigma^2 \gg \tau_{ij}$), as it is for real metabolic data, $\rho_{ij} \cong 1$ (i.e., all correlations between absolute metabolic values are large).

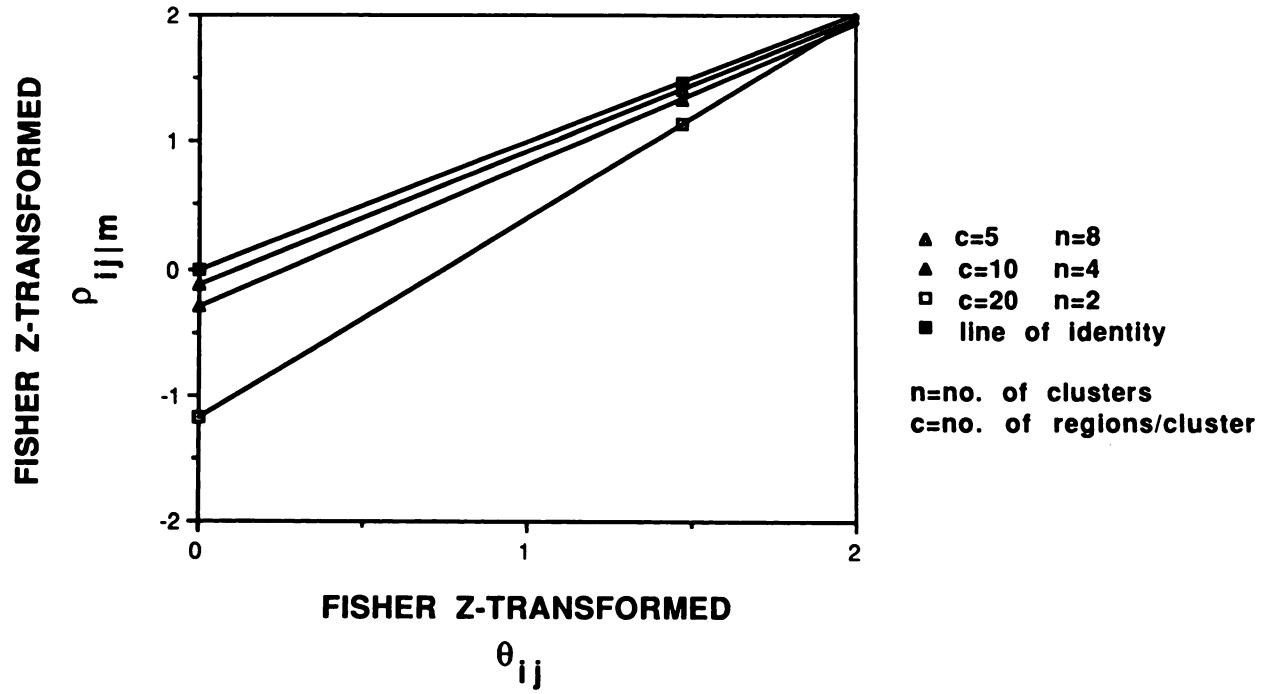

FIGURE 1
Graph comparing Fisher Z-transformed values of the intrasubject and partial correlation coefficients for the theoretical example of Ford (*1*). The line of identity has a slope of 1 and a y-intercept equal to 0. The y-intercept and slope for the best-fit regression lines, respectively, are the following: for c = 5, −0.13 and 1.05; for c = 10, −0.30 and 1.11; for c = 20, −1.18 and 1.58. Only when the number of regions per cluster is large (and hence the number of clusters is small) does the regression line not approximate the line of identity.

Horwitz et al. (*6*) suggested that partial correlations, controlling for global CMRglc, reasonably approximate θ_{ij}. Assume that

$$X_{rm} = \sum_{s=1}^{S} X_{rs}/S \qquad (6)$$

is an appropriate measure of global glucose utilization. The partial correlation coefficient between variables, controlling for global metabolism, is given by (*21*):

$$\rho_{ij|m} = \frac{\rho_{ij} - \rho_{im}\rho_{jm}}{\sqrt{(1 - \rho_{im}^2)(1 - \rho_{jm}^2)}}, \qquad (7)$$

where ρ_{ij} is given by Eq. (2) and ρ_{im} is the correlation coefficient between rCMRglc in region i and global CMRglc. Ford (*1*) shows that

$$\rho_{im} = \frac{\sigma^2 + \tau_{i\cdot}}{\sqrt{(\sigma^2 + \tau_{ii})(\sigma^2 + \tau_{\cdot\cdot})}} \qquad (8)$$

and $\tau_{i\cdot} = \sum_j \tau_{ij}/S$ and $\tau_{\cdot\cdot} = \sum_i\sum_j \tau_{ij}/S^2$.

Ford considers a theoretical example in which it is supposed there are data from 40 ROIs. He assumes that the 40 regions are arranged in n clusters, each cluster of size c (e.g., n = 5, c = 8 means that the 40 regions are divided into five clusters, each consisting of eight regions). He assumes, furthermore, that there is a strong metabolic coupling (θ_{ij} = 0.9) between all pairs of regions within a cluster, and a zero metabolic coupling (θ_{ij} = 0.0) between regions in different clusters. He then evaluates $\rho_{ij/m}$, the partial correlation coefficient between regions i and j, to see how closely it approximates θ_{ij}, the true intrasubject correlation.

Ford finds that when the number of regions within each cluster is less than ten, $\rho_{ij/m} \cong \theta_{ij}$, although $\rho_{ij/m}$ is negative, rather than zero, when $\theta_{ij} = 0$. For example, for c = 5, $\rho_{ij/m} = -0.13$ when $\theta_{ij} = 0$, and $\rho_{ij/m} = 0.89$ when $\theta_{ij} = 0.9$; for c = 10 (four clusters of ten regions each), the corresponding values for $\rho_{ij/m}$ are −0.29 and 0.87, respectively; for c = 20 (two clusters of 20 regions each), the respective values for $\rho_{ij/m}$ are −0.83 and 0.82. Thus, although positive partial correlation coefficients are reasonably correct, negative values arise when θ_{ij} = 0. Further, when there are few clusters, the negative partial correlations can become large in magnitude, thus suggesting a negative functional association where none exists. For this reason, Ford concludes that the use of partial correlation coefficients is misleading.

A way to assess quantitatively how closely partial correlation coefficients approximate the intrasubject correlations is the following. Each correlation coefficient is transformed by means of the Fisher Z-transformation to produce a set of numbers which are distributed in an approximately normal manner (*22*):

$$Z_{ij} = \tfrac{1}{2}\left[\log_e \frac{1 + r_{ij}}{1 - r_{ij}}\right] \qquad (9)$$

(Note: for intrasubject correlations, $r_{ij} = \theta_{ij}$; when the correlation coefficient is a partial, r_{ij} of Eq. (9) is $r_{ij/m}$). Pearson product moment correlations between the intrasubject and partial correlations (using the Z_{ij}'s as the elements entering the correlation) are calculated, as are the least square regression parameters. If the two sets of values approximate one another, then the correlation coefficient between them should be close to 1.0, the slope of the best-fit regression line should be near 1.0, and the y-intercept of the line should be near 0.0. The results of applying this procedure to the theoretical example of Ford (*1*) is shown in Figure 1. Only when the number of clusters is small [and the number of regions in each cluster is large (i.e., n = 2, c = 20)] does the regression line not have a slope close to 1 and a y-intercept near 0.

Although Ford (*1*) does not discuss why large artifactual negative correlations arise in his example, it is quite easy to see how they are generated. For this purpose, it is simpler to consider correlations among reference ratios of metabolic values (the reference ratio for region s in subject r is X_{rs}/X_{rm}). Consider the case with 2 clusters, each containing 20 regions. Let us see how reference ratios vary compared with absolute rates as we enter each subject's metabolic values into the evaluation of the correlation coefficient. Suppose we have a subject for whom one of the regions in the first cluster has a larger value of metabolism than for a second subject, although the metabolic values for regions in the second cluster are the same in the two subjects. Because each region in the first cluster is coupled strongly (by assumption) to every other region in that cluster, every one of its cluster-mates also will have a larger metabolic value. Furthermore, because half of the regions of the brain are in the first cluster, X_{rm} (the global average metabolic rate) also will be larger for the first than for the second subject. However, the reference ratio for each region in the second cluster will be diminished in the first subject relative to the second, because the denominator, X_{rm}, will have a larger value. As more subjects are entered into the calculation of the correlation coefficient, the net effect will be an apparent inverse relation between regions in the two clusters, giving a negative correlation between the reference ratios. Essentially, the same kind of argument applies to the partial correlation coefficient, with global mean metabolism as the controlled variable.

As this example shows, the source of the apparent negative correlation is the artificial division of the brain into two non-interacting clusters, each cluster containing regions strongly coupled to one another. Given what we know about the interactive nature of the brain (*2*), it is hard to envision a situation in which a large fraction of the brain increases its rate of metabolism without interacting, even indirectly, with the remainder of the brain. The more interesting case is that of selective activation of a small group of functionally coupled regions [e.g., (*23*)].

Nevertheless, the example provided by Ford (*1*) illustrates the need to not use the correlation method unthinkingly. As with all scientific techniques, there is a boundary of applicability beyond which a technique breaks down, and one part of science is finding that boundary. However, it is quite easy to determine if the particular condition used by Ford, which is beyond this boundary, occurs in real biological data. In his example, as we have seen, when there are two non-interacting clusters of 20 regions each, the partial correlation coefficients are either large and positive (0.82), or large and negative (−0.83). Therefore, a frequency histogram of all the partial correlation coefficients for this model would be sharply bimodal, as is illustrated in Figure 2A (where we have added some statistical spread to the peaks). A unimodal distribution would suggest that Ford's condition is not met. figure 2B shows the frequency histogram of partial correlation coefficients for the real metabolic data obtained from PET scans of healthy men in the resting state (eyes covered, ears plugged), and its unimodal character clearly indicates that Ford's condition is not applicable to this real case. Figure 4 of Soncrant et al. (*9*) shows a unimodal distribution of partial correlations obtained from rats in the resting state, so these animal data also do not meet Ford's condition.

Correlation Method for the Resting Brain: Partial Correlations Versus Absolute Correlations

In this section, we turn to real metabolic data obtained from PET scans of healthy men in the resting state (eyes covered, ears plugged) (*17–19*). Although we showed in the previous section how an artifactual negative correlation that arose in Ford's example represented an artificial situation, it is necessary to show that partial correlation coefficients for real brain metabolic data reasonably approximate the (unknown) intrasubject correlations.

As discussed above, if the intersubject variance (σ^2) is zero, correlation coefficients of absolute metabolic values give us intrasubject correlations. For the additive model of Eq. (1), the "subject effect", p_r, is the source of the between-subject variance. Therefore, in order to use correlations of absolute values to approximate intrasubject correlation coefficients, subjects who have approximately equal global CMRglc (so that p_r is the same for each subject) should be used.

The coefficient of variation (CV = 100 × s.d./mean) for CMRglc for the 60 men was 22.5%. From this original group of 60, we selected the 20 subjects whose CMRglc values ranged from 4.70 to 5.30 mg/100g/min, with a mean (±s.d.) of 5.06 (±0.18) mg/100g/min, thus giving us a group of subjects with a CV of 3.6%. This group of 20 subjects will be called the

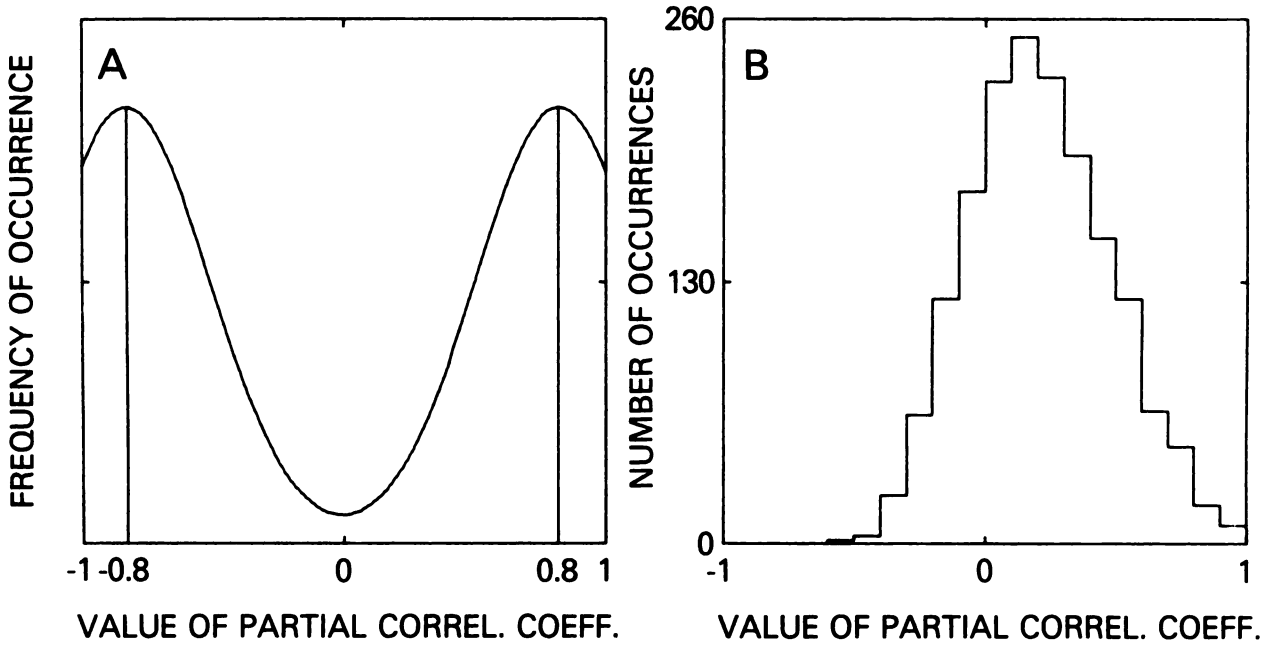

FIGURE 2

A: Frequency distribution of partial correlation coefficients for the example given by Ford (*1*), in which the brain is arranged in two clusters of strongly interacting regions, with no coupling between regions in different clusters. B: Frequency distribution of partial correlation coefficients (in which CMRglc is the controlled variable) for the original group of 60 healthy men. The bins are 0.1 units wide.

"homogeneous" group. There was no significant difference in CMRglc between the homogeneous group of 20 and the total group of 60 (Student's t-test, $p > 0.2$), nor was there a difference in mean age (Student's t-test, $p > 0.98$; for the group of 20, mean age was 48.1 (±19.5) yr, with range 20–83 yr).

The correlation matrix of absolute metabolic rates (referred to henceforth as the absolute correlation matrix) for the homogeneous group of 20 men should reflect closely the intrasubject correlation matrix, given that CMRglc has about the same value for each subject. To see if the intrasubject pattern of correlations is approximated by a partial correlation matrix (i.e., to determine if partial correlations provide a nondistorting correction for the "subject effect"), we constructed from the homogeneous group of 20 subjects an artificial group of 20 subjects. This artificial data set, constructed so that the additive data model of Eq. (1) holds, was obtained as follows: (a) the homogeneous group of 20 was arranged in order of ascending CMRglc; (b) −2.00 mg/100 g/min was subtracted from each of the 59 values of rCMRglc and from CMRglc for the subject with the lowest CMRglc; (c) −1.8 mg/100 g/min was subtracted in a similar way from the subject with the second lowest CMRglc; (d) this procedure was continued until the subject with the highest CMRglc was reached; this subject had 1.8 mg/100g/min added to each of his 59 rCMRglc values and CMRglc. For the artificial group of 20, CMRglc ranged between 2.70–7.10 mg/100g/min with a mean of 4.96 (±1.36) mg/100g/min, and a CV of 27.4%. Thus, mean CMRglc did not differ significantly between the original group of 60 men and this artificial group of 20.

Starting with the 59 values of rCMRglc for each subject, we calculated the 1,711 possible pairwise correlation coefficients. For the homogeneous group of 20, these were correlations of the absolute values of rCMRglc, whereas for the artificial group of 20, these were partial correlation coefficients, controlling for CMRglc. Because the data from the artificial group was constructed from the data of the homogeneous group, the absolute correlation matrix provides a "gold standard" by which we can judge how good an approximation are the partial correlation coefficients.

Following the quantitative comparison procedure used in the previous section, the Pearson product moment correlation between the Fisher Z-transformed values of the absolute and partial correlation coefficients was calculated, as were the least square regression parameters. The results are shown in Figure 3A. As can be seen, the partial correlations for the artificial group of 20 had a correlation of 0.965 with the absolute correlations for the homogeneous group of 20 subjects, and the slope of the regression line was 1.00. This shows that the intrasubject pattern of correlations is approximated by partial correlations, when the additive model of Eq. (1) holds.

Also compared (Fig. 3B) were the partial correlations for the original group of 60 and the correlations of absolute values for the homogeneous group of 20. For

this case, the correlation coefficient was 0.858 and the slope of the regression line was 0.686. As would be expected, the correspondence is not as good as with the artificial group, but is reasonably close (The best-fit regression line having a slope <1 probably is due to three factors.

1. Although the 20 subjects of the homogeneous group have approximately equal CMRglc, the between-subject variance is not equal exactly to zero, and by Eqs. (2) and (3), this means that each absolute correlation coefficient is larger than the intrasubject correlation it is meant to represent. This is not a large effect, but may have contributed somewhat to the partial correlations for the group of 60 having, on average, smaller values than the absolute correlations for the group of 20.

2. The homogeneous group of 20 may not be perfectly representative of the original group of 60. Unlike the comparison between the homogeneous and artificial groups, the homogeneous group cannot be taken as the "gold standard".

3. The variance associated with each correlation coefficient is skewed toward zero. This means that if more subjects are added to the sample, the chances are greater that the resulting correlation will be smaller (in magnitude) than that obtained from the first sample (e.g., if r = 0.99, adding more subjects can only make the correlation worse). The net effect is that the correlations for the original group of 60 will, on average, have smaller values than for the group of 20. This is probably the major factor contributing to the slope of the best-fit regression line having a slope less than one.) This result indicates that the partial correlation matrix for the original group of 60 is not artifactually distorted by use of partial correlation coefficients.

Thus, we have shown that the partial correlation method preserves the intrasubject correlational structure of subjects in the resting state.

Correlation Method for the Resting Brain: Partial Correlations Versus Reference Ratio Correlations

As noted above, some investigators have correlated reference ratios (e.g., rCMRglc/CMRglc) rather than partial correlation coefficients (*7,8,15*). The use of reference ratios is motivated by assuming that the underlying data are based on a multiplicative model (e.g., $X_{rs} = \mu_s p_r + \epsilon_{rs}$), rather than on an additive one, as in Eq. (1). Ford (*1*) suggests that the reference ratio approach may be as suspect as the partial correlation method. We have found during our previous studies (*6,9,13,14*) that the correlation matrices obtained with reference ratios are quite similar to those obtained with partial correlation coefficients (unpublished observations). In this section, we show this explicitly for the original group of 60 men.

As we did with the partial correlation matrices, we transformed each reference ratio correlation coefficient using Eq. (9), and calculated the correlation coefficients and the least square slopes and intercepts between the reference ratio correlation matrix on the one hand, and

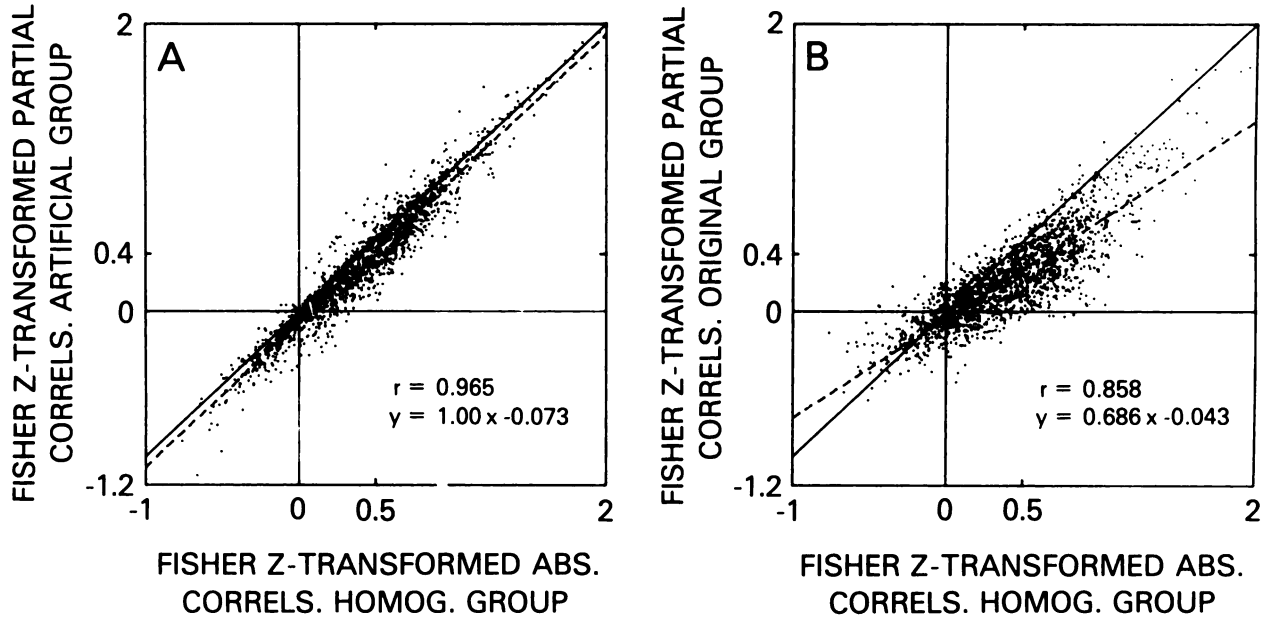

FIGURE 3

Graphs comparing corresponding Fisher Z-transformed values of the 1,711 pairwise correlation coefficients between two correlation matrices. In each case, the x-axis represents the absolute correlations for the homogeneous group of 20 men. In (A), the y-axis corresponds to the partial correlations for the artificial group of 20; in (B), the y-axis corresponds to the partial correlation coefficients for the original group of 60 men. The solid line is the 45° line, the dashed line is best-fit regression line whose parameters are displayed in the figures.

the partial correlation matrix and the absolute correlation matrix on the other. The results are illustrated in Figures 4A and 4B. The correspondence between the reference ratio and partial correlation matrices is strong (correlation coefficient = 0.97, slope = 0.97), whereas that between the reference ratio and absolute correlation matrices is as good as that found in the previous section between the partial and absolute correlation matrices.

Thus, for the resting state in healthy men, the reference ratio correlation matrix is quite similar to the partial correlation matrix; both provide good approximations of intrasubject correlations among metabolic rates. These results suggest that the correlational structure for the testing state is robust, and not strongly dependent on the underlying statistical model for the data.

DISCUSSION

The correlation method attempts to characterize the brain in terms of functional associations among brain regions. Because of a large "subject effect" on glucose utilization measurements, such that intraindividual differences in rCMRglc frequently are smaller than interindividual differences (*6*), some method must be employed to extract the intrasubject correlational pattern (θ_{ij}) from the interindividual correlational structure (ρ_{ij}). Partial correlation analysis (*6,9,13,14,16*), and reference ratio correlation analysis (*7,8,15*) have been used to achieve this end. Ford (*1*) criticized the use of partial correlations, and suggested that similar problems may affect the use of reference ratios. He demonstrated, using a specific theoretical example, that artifactual, large partial negative correlations might arise.

In this paper, we have shown that Ford's example, which gives rise to the artifactual negative correlations, although technically correct, is based on an intrasubject correlation pattern that is highly unlikely to occur, but can be detected, if present, by seeing if the frequency histogram of partial correlation coefficients has a bimodal distribution. Nevertheless, his analysis suggests that caution be used in attributing important neurobiological meaning to large negative correlations. Ford's example is useful in that it shows, in at least one condition, that the correlation matrix method has limitations.

We also demonstrated that in the resting state the partial correlation and the reference ratio correlation matrices contain values that correlates strongly with one another, and that each correlate strongly with a correlation matrix obtained by using absolute values of rCMRglc for a homogeneous group of subjects whose "subject effect" is essentially equal. Because the matrix for the homogeneous group closely represents the true intrasubject correlation pattern, these correspondences suggest that partial correlations, or reference ratio correlations, adequately approximate intrasubject correlation coefficients.

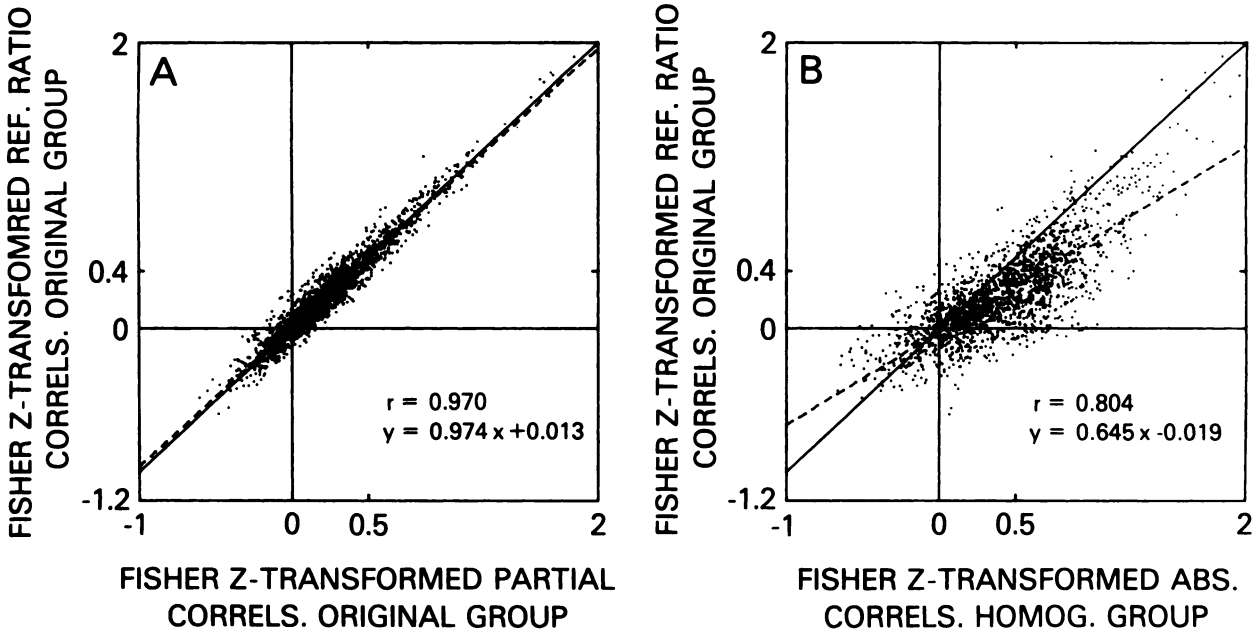

FIGURE 4
Graphs comparing corresponding Fisher Z-transformed values of the 1,711 pairwise correlation coefficients between two correlation matrices. In (A), the partial correlation coefficients for the original group of 60 (x-axis) and the reference ratio correlation coefficients for the group of 60 (y-axis) are compared. In (B), the absolute correlations for the homogeneous group of 20 (x-axis) and the reference ratio correlations for the group of 60 (y-axis) are compared. Solid and dashed lines are as in Figure 3. Values used for the best-fit regression line are displayed in the figures.

The above conclusions, shown to be valid for the resting state, must be tested for metabolic studies done during activation. Given that the distorted negative partial correlation coefficients in Ford's example depends on large-scale tight coupling across much of the brain, it is likely that partial correlations or reference ratio correlations will remain adequate if only a limited number of brain regions are activated. Of course, it is precisely these kinds of restricted activation studies that will shed the most light on functional interactions in the brain.

ACKNOWLEDGMENT

The authors thank Drs. Karen Pettigrew, James Haxby, Cheryl Grady, and Jay Luxenberg for useful discussions.

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