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A Linear Relationship Exists among Brain Diffusion Eigenvalues Measured by Diffusion Tensor Magnetic Resonance Imaging

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Diffusion in biological tissues can be measured by magnetic resonance diffusion tensor imaging The complex nature of anisotropic diffusion in the brain has been described by a diffusion tensor which contains information about the magnitude of diffusion in different directions. Each tensor contains a set of three eigenvalues which are related to the major, intermediate, and minor axes of a diffusion ellipsoid. This investigation demonstrates that the various sets of diffusion eigenvalues from different regions of the brain lie along a line in ordered eigenvalue space. Sets of ordered diffusion eigenvalues were considered points in ordered eigenvalue space. The line which best fit the data by minimizing the total squared deviations was determined. A new coordinate system was constructed through translation and rotation which spanned ordered eigenvalue space. Eigenvalues from both monkey brain and human brain were studied. It was found that the sets of eigenvalues from both species have significant linear trends. Moreover, the same line may describe the brain eigenvalues from both species. It is likely that this linear relationship of the eigenvalues observed in an ordered eigenvalue plot is related to a combination of (1) conservation of total isotropic diffusion and (2) the degree of orientational dispersion of the microfibers within each voxel. © 1999 Academic Press

Key Words: **diffusion; brain; diffusion tensor imaging; diffusion anisotropy.**

INTRODUCTION

Diffusion in biological tissues can be measured by magnetic resonance diffusion tensor imaging (*1–6*). Isotropic diffusion refers to the situation where the diffusivity is the same in all directions in space and can be described by a simple scalar quantity. Diffusion in the gray matter of the brain has been found to be relatively isotropic. However, in general, brain diffusion is not isotropic. Diffusion which varies with direction is termed anisotropic. The complex nature of anisotropic diffusion has been described by a diffusion tensor which contains information about the magnitude of diffusion in different directions. This information is often depicted as a diffusion ellipsoid oriented in space with the major axis in the direction of greatest diffusion. The major, intermediate, and minor axes are mutually orthogonal.

A set of eigenvalues of a diffusion tensor contains λ_1, λ_2, λ_3. These eigenvalues are expressed in square millimeters per second. They can be ordered by decreasing magnitude as $\lambda_{max} \geq \lambda_{int} \geq \lambda_{min} \geq 0$. The set of ordered eigenvalues can be considered a point in a three dimensional space denoted by $\boldsymbol{\lambda}(i)$,

$$\boldsymbol{\lambda}(i) = \begin{bmatrix} \lambda_{max}(i) \\ \lambda_{int}(i) \\ \lambda_{min}(i) \end{bmatrix}, \qquad [1]$$

where i ranges from 1 to n, the total number of sets of eigenvalues.

Ordered eigenvalue space is composed of all possible values of the ordered eigenvalues. This space has the shape of an inverted triangular pyramid with the apex at the origin. The planes that form the boundaries are $\lambda_{min} = 0$, $\lambda_{min} = \lambda_{int}$, and $\lambda_{int} = \lambda_{max}$.

In this investigation it will be demonstrated that the sets of eigenvalues, $\boldsymbol{\lambda}(i)$, from regions of brain parenchyma lie along a line in ordered eigenvalue space. This line will be defined and characterized by the use of a coordinate system translation and rotation. The new coordinate system is a natural system for describing the eigenvalues. It allows convenient parameters for describing position along the line and deviations from the line. This new parameterization may prove to be useful for detecting and characterizing abnormal values of diffusion in tissues.

MATERIALS AND METHODS

The Mathematica software package (Wolfram Research, Inc., Champaign, IL) was used on an Apple Quadra computer (Apple Computer Inc., Cupertino, CA) to perform the mathematics and analyze the data in this manuscript.

Overview

The coordinate system described above containing $\boldsymbol{\lambda}(i)$ will be referred to as the "original ordered eigenvalue coordinate

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system." A new coordinate system spanning ordered eigenvalue space will be derived below.

By translocation and rotation of the original coordinate system, one of the new axes, the *s* axis, will be the line which best describes the linear trend in the values $\boldsymbol{\lambda}(i)$ from the brain parenchyma.

Determination of the Line Which Best Fits the $\boldsymbol{\lambda}(i)$

The data points $\boldsymbol{\lambda}(i)$ were projected onto a plane in original eigenvalue space. The variance of the projected points was determined (the total of the squared distances from the center of mass). Then, by use of an iterative method, the plane, *P*, which minimized the variance, was identified.

Let $L(s)$ be the line which is orthogonal to *P* and which also passes through the center of mass of the points projected onto *P*. Then $L(s)$ best describes the linear trend of the brain parenchymal points $\lambda(i)$.

Determination of the Origin of the New Coordinate System

$L(s)$ crosses the boundary of the original ordered eigenvalue space at a point **q,** which will be the origin of the new coordinate system. The point, **q,** was found to be in the plane $\lambda_{max} = \lambda_{int}$.

Translation and Rotation of the Coordinate System

Let $\mathbf{u}_1$ be the unit vector orthogonal to the plane *P*. Then the line

$$L(s) = \mathbf{q} + \mathbf{u}_1 s \qquad [2]$$

best describes the linear trend in $\boldsymbol{\lambda}(i)$. $\mathbf{u}_1$ is the unit basis vector for the new *s* axis.

Two other unit vectors, $\mathbf{u}_2$ and $\mathbf{u}_3$, can be arbitrarily defined to be orthogonal to $\mathbf{u}_1$ and also mutually orthogonal ($\mathbf{u}_2$ uses the Gram–Schmidt orthogonalization process),

$$\mathbf{u}_2 = (\mathbf{q} - (\mathbf{u}_1 \cdot \mathbf{q})\mathbf{u}_1)/\mathrm{Norm}(\mathbf{q} - (\mathbf{u}_1 \cdot \mathbf{q})\mathbf{u}_1), \qquad [3]$$

$$\mathbf{u}_3 = \mathbf{u}_1 \times \mathbf{u}_2, \qquad [4]$$

where $\cdot$ denotes the dot or inner product, $\times$ denotes the cross product, and "Norm" is the square root of the sum of squared elements of the vector. The *t* axis was chosen as $\mathbf{u}_2$ in Eq. [3] such that it was along the line orthogonal to $L(s)$ which intersects the origin.

The matrix R^{-1} is defined as

$$R^{-1} = [\mathbf{u}_1\ \mathbf{u}_2\ \mathbf{u}_3]. \qquad [5]$$

Then the 3×3 unitary rotation matrix *R* (the inverse of R^{-1}) transforms the original coordinate system into the new transformed coordinate system

$$\boldsymbol{\lambda}'(i) = R(\boldsymbol{\lambda}(i) - \mathbf{q}). \qquad [6]$$

The axes in the transformed coordinate system are referred to as *r*, *s*, and *t*.

$$\boldsymbol{\lambda}'(i) = \begin{bmatrix} s(i) \\ t(i) \\ r(i) \end{bmatrix}. \qquad [7]$$

$\boldsymbol{\lambda}'(i)$ can be written in a cylindrical coordinate system, (s, δ, ψ). δ is the distance of a point to the *s* axis and ψ is the angle from the *t* axis in the *r*–*t* plane. *r*, *s*, *t*, and δ are expressed in square millimeters per second, ψ in degrees.

The goodness of fit of the line to the data was measured by the coefficient of determination, r^2, with $0 \le r^2 \le 1$ (*7*). It equals the sum of the squared distances from the predicted values to the mean of the data points divided by the sum of the squared distances from the data points to their mean. r^2 is the fraction of the variation in the data points which can be accounted for by the fitted line.

Brain Eigenvalues Used in the Derivation

Mean eigenvalues from regions of interest drawn in various brain regions are available in the literature. In the present investigation, eigenvalues from regions of interest in human brain (*2*) and monkey brain (*3*) were combined and fitted as described above. The eight eigenvalues from monkey brain parenchyma represent mean values derived from pooled regions of interest in the right and left hemispheres of six animals. The eight eigenvalues from human brain are similarly derived from eight healthy volunteers. The lines describing the linear relationship between the eigenvalues from each species were fitted separately. The human brain eigenvalue from the frontal cortex was found to deviate significantly from the line fitted to the other human brain eigenvalues. Using the r_{11} outlier analysis procedure (*8*) the probability that this point is an outlier exceeds 0.98. Therefore, this point was rejected from use in the analysis. In the original article (*2*) Pierpaoli *et al.* also considered the frontal cortex point to be an outlier and suggested that it might be due to partial volume contamination by cerebral spinal fluid.

RESULTS

Table 1 shows highly linear trends with r^2 values near 1 for the best line fit to the monkey data (monkey fit–monkey data) and for the best fit line to the human data (human fit–human data).

Table 1 also shows the r^2 value when the best fitting line to the monkey is applied to the human data (monkey fit–human data), and vice versa. A *t*-test was performed to determine whether there was significant difference in how each line fit the

TABLE 1
r^2 Values from Various Line Fits to the Data

	Monkey data	Human data	Combined data
Monkey fit	0.99	0.96	
Human fit	0.99	0.97	
Overall fit			0.97

data sets. The value of r^2 for human fit–human data was compared to r^2 for the monkey fit–human data. Using the *t*-test described by (*9*) the values of r^2 were not significantly different ($p > 95\%$). In the comparison of monkey fit–monkey data to human fit–monkey data it was slightly less likely that the two values of r^2 were identical ($p > 85\%$). This is due to the extremely good fit of the monkey line to the monkey data ($r^2 = 0.99$). These results demonstrate that both sets of eigenvalues are well described by either regression line. Therefore, the eigenvalues from both monkey brain and human brain were combined. A best fit line for the combined data sets was determined. This line was found to also have a significant linear trend (overall fit–combined data in Table 1).

Based on the combined data set, the rotation matrix for coordinate system transformation is

$$R = \begin{bmatrix} 0.86 & -0.34 & -0.38 \\ 0.50 & 0.69 & 0.52 \\ 0.083 & -0.64 & 0.77 \end{bmatrix}. \quad [8]$$

Figures 1a–c show plots of the original eigenvalue points and the best fitting line (the *s* axis). Inspection of the deviations of the points from the *s* axis demonstrates a small higher order trend in the residuals. However, the linear transformation and rotation used in this investigation cannot incorporate these higher order terms.

In the original coordinate system, the equation for $L(s)$ is

$$L(s) = \begin{bmatrix} \lambda_{max} \\ \lambda_{int} \\ \lambda_{min} \end{bmatrix}(s) = \begin{bmatrix} 734 \\ 734 \\ 532 \end{bmatrix} + \begin{bmatrix} 0.86s \\ -0.34s \\ -0.38s \end{bmatrix} \times 10^{-6}\ \text{mm}^2/\text{s}. \quad [9]$$

Values of the parameter *s* for different brain regions are tabulated in Table 2. These values are based on the best fit to the combined set of eigenvalues. When listed in ascending order of *s*, the anatomic regions are ordered according to expected degree of anisotropy. It is noteworthy that similar anatomic regions from human and monkey data (i.e., the corpus callosum) have similar values of *s*. The great similarity in *s* values for brain regions between species suggests that the method is robust. Differences between individuals within a species are expected to be much less than those between species.

DISCUSSION

Many measures have been used to convert the tensor, which describes complex diffusion in a volume of tissue, into a set of meaningful scalar quantities. Scalar representation of some attribute of the tensor is more readily comprehensible than the full tensor itself and can be easily displayed as a parametric image. These measures have described diffusion magnitude, anisotropy, and skewness (*1–6, 10*). Most of these measures define planes or surfaces of isometric values in three dimensional eigenvalue space. Table 1 demonstrates that *s* can be considered an anisotropy measure because the magnitude of parameter *s* correlates with the expected degree of anisotropy in different anatomic regions. However, the present derivation is much more than just the proposal of another anisotropy measure. It is a model of the relationship between brain eigenvalues in normal tissue.

If the eigenvalues of the diffusion tensor associated with each imaging voxel had magnitudes which were randomly distributed, then the ordered eigenvalue plot of the eigenvalues from all the voxels would have points distributed throughout the space. If there were a single constraint on the allowable eigenvalues, such as constant total isotropic diffusion, then the points in an ordered eigenvalue plot would fall on a plane. However, the present investigation demonstrates that the points in an ordered eigenvalue plot fall along a line. This suggests that there are at least two constraints on the values of the three eigenvalues for each voxel. A possible explanation for this observed linear relationship relates the observation to the tissue microstructure. On a microscopic level, brain is composed of fibers with a preferred direction of diffusion along the fiber (rather than across it). Some tissues are composed of fibers which are highly parallel, such as the corpus callosum. Other brain structures, some white matter structures and most of the gray matter structures, have a more dispersed distribution of microfiber orientations. It is likely that the linear relationship of the eigenvalues observed in an ordered eigenvalue plot is related to a combination of (1) conservation of total isotropic diffusion and (2) the degree of orientational dispersion of the microfibers within each voxel, perhaps with similar microscopic diffusion within the region of each individual microfiber. The parameter s is likely related to the degree of microfiber dispersion with the voxel. A future direction for research would be to construct a mathematical model based on these assumptions to assess whether it predicts the observed linear eigenvalue relationship.

The monkey and human brain eigenvalue data sets were combined because they were derived from the same laboratory with similar methodologies. However, there may have been subtle differences in technique between the two studies because these two investigations were not necessarily undertaken for the purpose of this comparison. Therefore, future studies with human subjects, monkeys, and other animals, with careful attention to the maintenance of identical procedures, are nec-

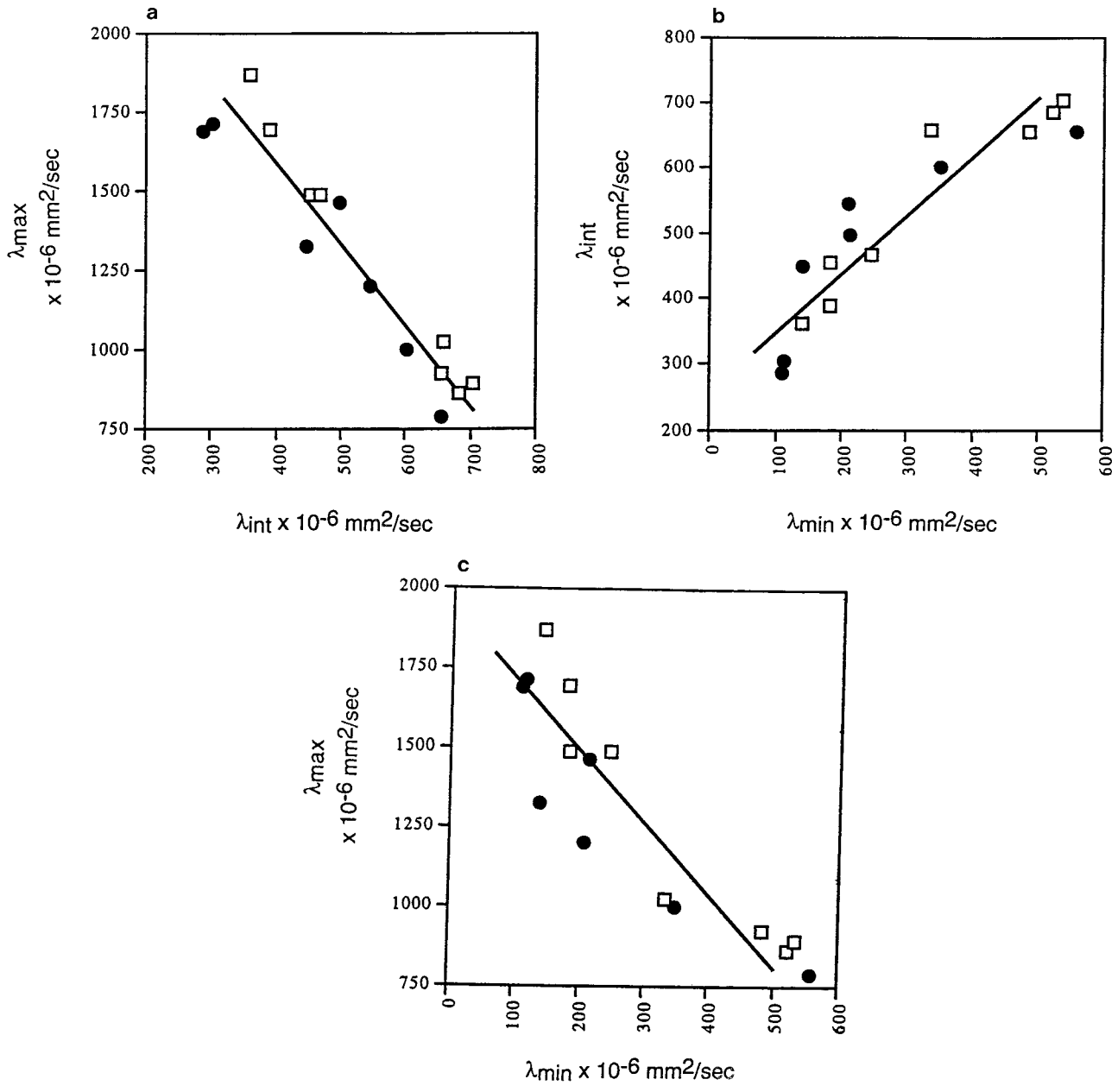

FIG. 1. (a) A plot of the projection of the eigenvalue plots onto the λ_{int}–λ_{max} plane. The projection of the best fit line, fitted to the combined monkey and human data set, is also shown. The points from the monkey brain (open squares) and human brain (filled circles) are plotted with different symbols although the combined set of eigenvalues was used when determining the best fitting line. (b) A plot of the projection of the eigenvalue plots onto the λ_{min}–λ_{int} plane. The projection of the best fit line is also shown. (c) A plot of the projection of the eigenvalue plots onto the λ_{min}–λ_{max} plane. The projection of the best fit line is also shown.

essary to verify that the diffusion eigenvalues from multiple species lie along the same line in ordered eigenvalue space.

Since normal tissues lie along $L(s)$, deviation of $\boldsymbol{\lambda}(i)$ from the line might denote pathology. Pathology could also be manifested by movement along the line in such a manner that the value of parameter s does not correspond to the normal value for that anatomic region.

The model identified the human frontal cortex eigenvalues (*2*) as outlier values. The same conclusion was reached in the original article. The ability to differentiate accurate diffusion eigenvalues from outliers strengthens confidence in the model and its ability to identify pathology.

If it is verified that the proposed model represents diffusion in normal brain tissue, projecting the diffusion eigenvalues

TABLE 2
Brain Regions and Their Corresponding Parameter *s*

Region	Species	Parameter *s*
Caudate nucleus	Human	59
Putamen	Monkey	130
Caudate	Monkey	143
Parietal cortex	Monkey	206
Centrum semiovale	Human	339
Subcortical Wt matter	Monkey	346
U fibers	Human	588
Posterior limb IC	Human	751
Optic radiation	Human	827
Anterior limb IC	Monkey	844
Posterior limb IC	Monkey	876
Corpus callosum	Monkey	1073
Splenium CC	Human	1131
Pyramidal tract	Human	1143
Optic tract	Monkey	1247

Note. IC = internal capsule, CC = corpus callosum, Wt = white. *s* has units $\times 10^{-6}$ mm^2/s.

onto the line could be used as a method of reducing measurement noise in normal tissues.

The trace of the diffusion tensor is commonly used as a measure of total diffusion. It is equal to three times the average of the diffusion tensor eigenvalues,

$$\lambda_{mean} = \text{trace}/3 = (\lambda_{min} + \lambda_{int} + \lambda_{max})/3. \qquad [10]$$

By use of the values from Eq. [9], λ_{mean} was calculated for the values of s (0–1300 $\times 10^{-6}$ mm^2/s in Table 2)) corresponding to the published normal tissue eigenvalues. This indicates that the model line lies nearly parallel to an isometric surface of the parameter λ_{mean}. The value of λ_{mean} for the largest s value in the brain regions tested ($s = 1247$) is only 8% larger than the λ_{mean} for the smallest s ($s = 59$), 670 $\times 10^{-6}$ mm^2/s versus 726 $\times 10^{-6}$ mm^2/s. The relatively constant λ_{mean} values agree with published observations (*2, 3*).

It is of note that the line $L(s)$ does not pass through a region of isotropy (such that $\lambda_{min} = \lambda_{int} = \lambda_{max}$). However, it is likely that this is due to a bias introduced by sorting the eigenvalues according to magnitude. Further investigation is necessary to determine the effect of this sorting bias. The small nonlinear trend noted in the residual values of the fitted line is also likely to be related to a bias introduced by ordering the eigenvalues.

As s increases (i.e., as the diffusion ellipsoid becomes more anisotropic) the value of the ratio $\lambda_{min}/\lambda_{int}$ increasingly deviates from unity. Similarly, the ratio $\lambda_{int}/\lambda_{max}$ departs from unity as s increases. Thus, the present model seems to suggests that the diffusion ellipsoid in normal brain tissue is not axisymmetric. However, further investigation is needed to verify this suggested finding because it could be inaccurate due to bias introduced by ordering the eigenvalues.

A bias is introduced into the eigenvalues by ordering. This bias is most severe for nearly isotropic sets of eigenvalues and least severe for very anisotropic sets of eigenvalues. The line fitted to the data reflects the presence of this bias. Perhaps a less biased estimation of the linear trend can be obtained by constructing a line which passes through only two points. One point is assumed to be exactly isotropic with the eigenvalues equal to the average λ_{int} from five gray matter regions (caudate, caudate, putamen, frontal cortex, and parietal cortex). The other point is very anisotropic with coordinates equal to the mean of five white matter tracts (splenium, corpus callosum, optic tract, posterior limb of internal capsule, and pyramidal tract). Using these values, an estimate of the "unbiased" line is

$$L_{unbiased}(s) = \begin{bmatrix} 701 \\ 701 \\ 701 \end{bmatrix} + \begin{bmatrix} 0.83s \\ -0.29s \\ -0.47s \end{bmatrix} \times 10^{-6}\ \text{mm}^2/\text{s}. \qquad [11]$$

CONCLUSIONS

In the present investigation the brain diffusion eigenvalue parameters $\boldsymbol{\lambda}(i)$ from both monkey and human are shown to demonstrate significant linear trends. Moreover, this study suggests that the linear trend found in both species can be described by the same line. This line describing the linear trend is a model for normal brain diffusion. It can be applied to measurement noise reduction. It can serve as an anisotropy measure. It may be useful for the detection of pathology in brain tissues. The observed linear relationship among the diffusion eigenvalues in the normal primate brain might be related to a combination of (1) the constant value observed for total isotropic diffusion throughout the brain, and (2) the degree of dispersion of the orientation of the microstructural elements within each voxel.

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