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Microstructural and Physiological Features of Tissues Elucidated by Quantitative-Diffusion-Tensor MRI

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Quantitative-diffusion-tensor MRI consists of deriving and displaying parameters that resemble histological or physiological stains, i.e., that characterize intrinsic features of tissue microstructure and microdynamics. Specifically, these parameters are objective, and insensitive to the choice of laboratory coordinate system. Here, these two properties are used to derive intravoxel measures of diffusion isotropy and the degree of diffusion anisotropy, as well as intervoxel measures of structural similarity, and fiber-tract organization from the effective diffusion tensor, $\underline{D}$, which is estimated in each voxel. First, $\underline{D}$ is decomposed into its isotropic and anisotropic parts, $\langle D \rangle \underline{I}$ and $\underline{D} - \langle D \rangle \underline{I}$, respectively (where $\langle D \rangle$ = Trace($\underline{D}$)/3 is the mean diffusivity, and $\underline{I}$ is the identity tensor). Then, the tensor (dot) product operator is used to generate a family of new rotationally and translationally invariant quantities. Finally, maps of these quantitative parameters are produced from high-resolution diffusion tensor images (in which $\underline{D}$ is estimated in each voxel from a series of 2D-FT spin-echo diffusion-weighted images) in living cat brain. Due to the high inherent sensitivity of these parameters to changes in tissue architecture (i.e., macromolecular, cellular, tissue, and organ structure) and in its physiologic state, their potential applications include monitoring structural changes in development, aging, and disease.

INTRODUCTION

Diffusion-tensor MRI (DT-MRI) is an MR imaging modality that provides unique microstructural and physiological information [contained in the six independent components of the diffusion tensor, $\underline{D}$, and the T_2-weighted amplitude, $A(0)$]. DT-MRI also presents new challenges, one of which is to extract and display this information. One approach we used previously was to construct three-dimensional fiber maps and diffusion ellipsoid images (*1*) which highlight the three-dimensional character of diffusion in tissues and other media. Another approach, which we employ here, is to summarize (or contract) the information embodied in the six independent elements of $\underline{D}$ by deriving a new set of *scalar* quantities that measure distinct, intrinsic microstructural features of diffusion within tissues (and other media) with which we can help assess its physiologic state.

Quantitative-diffusion-tensor MRI, which we introduce here, consists of deriving and displaying new quantitative scalar parameters (from the effective diffusion tensor, $\underline{D}$) that measure different intrinsic features of heterogeneous, anisotropic media. These imaging parameters characterize diffusion isotropy, diffusion anisotropy, macrostructural similarity, and fiber-tract organization. We call them "quantitative" because each parameter behaves like a quantitative histological or physiological stain.[1] In addition, we establish general criteria and a framework for constructing other intrinsic quantitative imaging parameters from the diffusion tensor.

MRI parameters that are now used to characterize diffusion in anisotropic media are not quantitative. Specifically, they are exquisitely sensitive to the choice of the laboratory coordinate system and to the applied imaging and diffusion gradient pulse sequences. As a result, they have little value in drug evaluation studies, multisite studies, or retrospective studies of a single patient. Quantitative diffusion tensor MRI overcomes these deficiencies.

When the translational mobility of a diffusing molecule depends upon a medium's orientation, diffusion is anisotropic. In biological tissues such as brain white matter, skeletal muscle, kidney, and cardiac muscle [e.g., see (*2*)], we ascribe anisotropic diffusion (as measured by MR spectroscopy or imaging) to the presence of heterogeneous but spatially ordered macromolecular, membranous, and cellular compartments. On the scale of a macroscopic voxel, it is appropriate to use an effective diffusion tensor, $\underline{D}$, to characterize diffusion anisotropy (*3*). In such anisotropic media, we use diffusion tensor MRI (*1*) to estimate an effective diffusion tensor in each voxel, as well as to calculate its principal (orthotropic) directions and principal diffusivities. The former are the mutually perpendicular, preferred directions along which molecular displacements of the spin-labeled molecules are uncorrelated, while the latter are the diffusivities along these preferred directions. We then use

[1] The use of the term "stain" in connection with an NMR contrast mechanism was first brought to our attention by Professor G. Allan Johnson.

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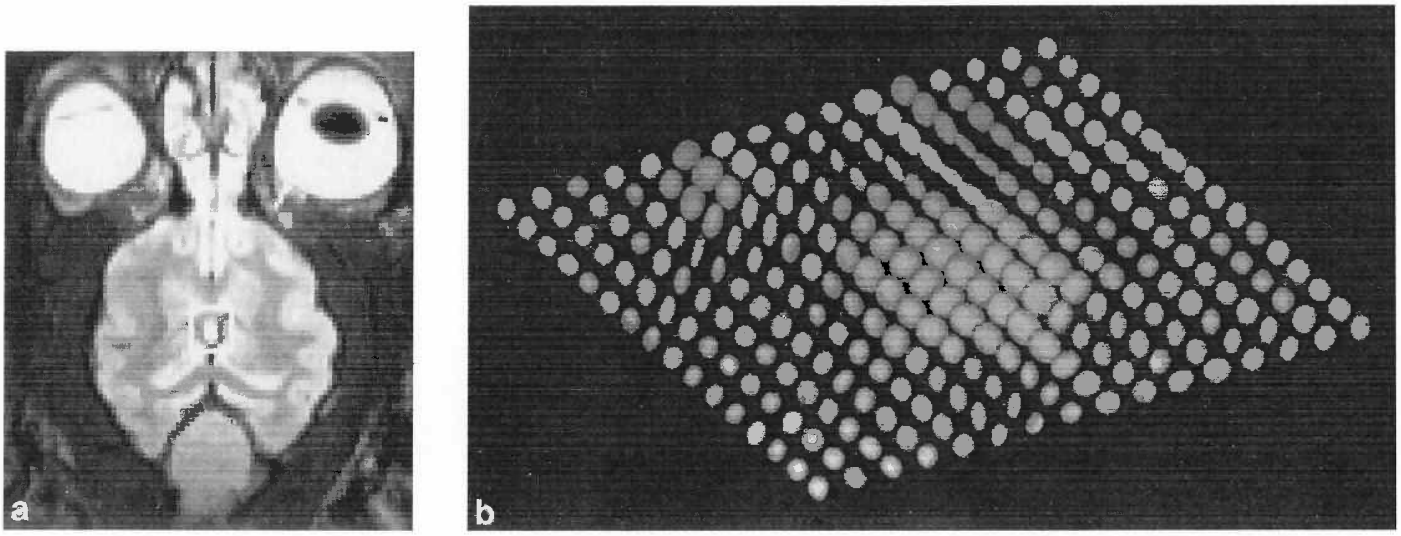

FIG. 1. (a) T_2-weighted image showing regions of gray matter, white matter, and CSF-filled ventricles in *in vivo* cat brain. (b) Diffusion ellipsoid image constructed from the effective diffusion tensor, $\underline{D}$, estimated in each voxel for the ROI enclosed by the white rectangle.

these quantities to derive measures of diffusion isotropy, diffusion anisotropy, macrostructural similarity, and fiber-tract organization.

To make the qualitative differences between these terms clear, consider the T_2-weighted image of living cat brain in Fig. 1a and the corresponding diffusion ellipsoid image (constructed for an ROI containing the internal capsule) in Fig. 1b. In principle, an image of a diffusion anisotropy index of this ROI should show the same contrast in voxels containing similar types of white matter, irrespective of their fiber-tract direction. This is because an anisotropy index should measure the degree of preferential mobility within a voxel, but should be insensitive to the direction along which diffusion is preferred. Geometrically, it should characterize the shape of the diffusion ellipsoid, but not its size or orientation. A measure of macrostructural (diffusive) similarity should identify tissues with a similar microstructure, specifically with similar principal directions and principal diffusivities. We expect that such a measure would be large in gray matter and larger still in the CSF-filled ventricles (where diffusion is largely isotropic), but it would not necessarily be large in regions containing white-matter fibers whose fiber direction is changing. Geometrically, a measure of structural similarity should measure the similarity of the shape, size, and orientation of different diffusion ellipsoids. Our definition of fiber-tract organization combines notions of diffusion anisotropy and macrostructural similarity. Fiber-tract organization is a property that we wish to ascribe only to anisotropic media (like white matter) but not to isotropic media (like the CSF-filled ventricles or most gray matter). Essentially, this parameter should measure the macrostructural similarity of the anisotropic part of the diffusion tensor in different voxels. Such a measure should highlight regions like the corpus callosum or the optical tract (where white-matter fiber tracts are packed in orderly bundles), but should show no fiber-tract organization in voxels containing isotropic media, such as gray matter and CSF-filled ventricles. In summary, these new one-dimensional (scalar) measures would provide new information about the three-dimensional character of diffusion in anisotropic tissues, information that has not been available using other MRI techniques.

We expect these parameters to be useful in elucidating structural features in normal, diseased, or degenerating tissues. The transformation of less-ordered to ordered, complex structures is a characteristic of normal development. This transformation occurs at a variety of length scales, including macromolecular (e.g., in neurofilaments and microtubules), cellular (e.g., in axons), tissue (e.g., in skeletal muscle, tendons, ligaments, and lens), and organ (e.g., in brain white matter, heart, and kidney). Moreover, preliminary findings that diffusion-weighted images are sensitive to architectural changes in the optic nerve prior to myelin deposition (*4*) suggest that these new parameters could be useful in assessing and characterizing normal and pathological developmental processes. Interest continues to grow in assessing developmental changes, particularly when induced by genetic manipulation or environmental stress. Noninvasive and nondestructive MRI techniques that can sense these changes may become increasingly valuable in such basic studies.

Conversely, the loss or lack of organization and structure at the molecular, cellular, tissue, and organ length scales is a characteristic of abnormal development, aging, or degeneration. For example, cardiac muscle fiber disorganization accompanies idiopathic cardiac myopathy and is believed to contribute to the loss of mechanical stiffness and pumping efficiency of the heart (*5*). A measure of the degree of fiber disorganization may be useful in diagnosing such pathologies, as also described by Wedeen *et al.* (*6*). Tumors in