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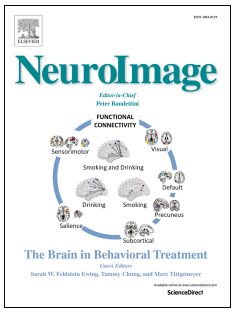

Magnetic resonance microdynamic imaging reveals distinct tissue microenvironments

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Magnetic resonance microdynamic imaging reveals distinct tissue microenvironments

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Abstract

Magnetic resonance imaging (MRI) provides a powerful set of tools with which to investigate biological tissues noninvasively and *in vivo*. Tissues are heterogeneous in nature; an imaging voxel contains an ensemble of different cells and extracellular matrix components. A long-standing challenge has been to infer the content of and interactions among these microscopic tissue components within a macroscopic imaging voxel. Spatially resolved multidimensional relaxation–diffusion correlation (REDCO) spectroscopy holds the potential to deliver such microdynamic information. However, to date, vast data requirements have mostly relegated these type of measurements to nuclear magnetic resonance applications and prevented them from being widely and successfully used in conjunction with imaging. By using a novel data acquisition and processing strategy in this study, spatially resolved REDCO could be performed in reasonable scanning times with excellent prospects for clinical applications. This new MR imaging framework—which we term "magnetic resonance microdynamic imaging (MRMI)"—permits the simultaneous noninvasive and model-free quantification of multiple subcellular, cellular, and interstitial tissue microenvironments within a voxel. MRMI is demonstrated with a fixed spinal cord specimen, enabling the quantification of microscopic tissue components with unprecedented specificity. Tissue components, such as axons, neuronal and glial soma, and myelin were identified on the basis of their multispectral signature within individual imaging voxels. These tissue elements could then be composed into images and be correlated with immunohistochemistry findings. MRMI provides novel image contrasts of tissue components and a new family of microdynamic biomarkers that could lead to new diagnostic imaging approaches to probe biological tissue alterations accompanied by pathological or developmental changes.

Keywords: MRI, microdynamic, relaxation, diffusion, spectroscopy, glia, model-free, MADCO, relaxometry

1. Introduction

Diffusion magnetic resonance imaging (dMRI) provides a means to investigate biological tissue microstructure, organization, and architecture (Johansen-Berg and Behrens, 2013). These techniques are sensitive to features of the net displacement distribution of water molecules within the sample (Stejskal and Tanner, 1965), providing powerful tools to explore microscopic domains quantitatively (Price, 2009). In conjunction with tissue models, dMRI experiments can be used to infer macroscopic (Basser et al., 1994, 2000) and microscopic (Burcaw et al., 2015; Szczepankiewicz et al., 2015; Benjamini et al., 2016) structural features, on the basis of the type and scale of physical barriers that are present in heterogeneous biological tissue.

MRI can also be sensitized to features of the local chemical environment and various dynamic relaxation processes, known as longitudinal and transverse relaxation, characterized by relaxation times, T_1 and T_2, respectively. Methods have been developed that do not assign a single, average relaxation time to each voxel but rather measure the distribution of the relaxation times within the volume (Whittall and MacKay, 1989; Kleinberg and Horsfield, 1990). This approach provides a one-dimensional (1D) distribution of T_1, T_2 or the apparent diffusivity, D, and it therefore implies a multicomponental tissue structure. These methods are usually referred to as nuclear magnetic resonance (NMR) relaxometry and are mainly used to characterize soil, rock, soft matter porous media (Whittall and MacKay, 1989; Kleinberg and Horsfield, 1990; Fordham et al., 1995), and *ex vivo* biological tissue (Beaulieu et al., 1998; Peled et al., 1999; MacKay et al., 2006).

Combining multidimensional MR contrast mechanisms, e.g., D-T_2, would provide novel and complementary information about dynamic molecular processes and microscopic physical and chemical environments within tissue. To date, these multidimensional relaxation–diffusion correlation (REDCO) spectroscopy experiments have been primarily relegated to applications involving NMR studies in homogeneous samples (Silva et al., 2002; Galvosas and Callaghan, 2010; Bernin and Topgaard, 2013; Song et al., 2016). However, apart from a few studies (Zhang and Blümich (2014); Tax et al. (2017); Kim et al. (2017)), these methods have not been widely used in MRI applications owing to the vast amount of scan time and acquired MR data required to reconstruct a single multidimensional spectrum.

A few studies have demonstrated integration of two-dimensional (2D) D-T_2 or T_1-T_2 spectroscopy with imaging of biological tissue. Does and Gore resolved three components within a region of interest (ROI) in peripheral nerve using a T_1-

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