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High-resolution three-dimensional macromolecular proton fraction mapping for quantitative neuroanatomical imaging of the rodent brain in ultra-high magnetic fields

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ABSTRACT

A well-known problem in ultra-high-field MRI is generation of high-resolution three-dimensional images for detailed characterization of white and gray matter anatomical structures. T_1-weighted imaging traditionally used for this purpose suffers from the loss of contrast between white and gray matter with an increase of magnetic field strength. Macromolecular proton fraction (MPF) mapping is a new method potentially capable to mitigate this problem due to strong myelin-based contrast and independence of this parameter of field strength. MPF is a key parameter determining the magnetization transfer effect in tissues and defined within the two-pool model as a relative amount of macromolecular protons involved into magnetization exchange with water protons. The objectives of this study were to characterize the two-pool model parameters in brain tissues in ultra-high magnetic fields and introduce fast high-field 3D MPF mapping as both anatomical and quantitative neuroimaging modality for small animal applications. In vivo imaging data were obtained from four adult male rats using an 11.7 T animal MRI scanner. Comprehensive comparison of brain tissue contrast was performed for standard R_1 and T_2 maps and reconstructed from Z-spectroscopic images two-pool model parameter maps including MPF, cross-relaxation rate constant, and T_2 of pools. Additionally, high-resolution whole-brain 3D MPF maps were obtained with isotropic 170 μm voxel size using the single-point synthetic-reference method. MPF maps showed 3-6-fold increase in contrast between white and gray matter compared to other parameters. MPF measurements by the single-point synthetic reference method were in excellent agreement with the Z-spectroscopic method. MPF values in rat brain structures at 11.7 T were similar to those at lower field strengths, thus confirming field independence of MPF. 3D MPF mapping provides a useful tool for neuroimaging in ultra-high magnetic fields enabling both quantitative tissue characterization based on the myelin content and high-resolution neuroanatomical visualization with high contrast between white and gray matter.

1. Introduction

An increase of magnetic field strength in MRI offers improvements of contrast in certain applications including functional, perfusion, and susceptibility-weighted imaging and a greater signal-to-noise ratio (SNR), which potentially can be converted into higher spatial resolution (Balchandani and Naidich, 2015; Lövblad et al., 2012; Ugurbil, 2014). However, imaging in ultra-high magnetic fields imposes a number of challenges, such as increased non-uniformity of B_0 and B_1 fields, larger specific absorption rate (SAR),

Abbreviations: MPF, macromolecular proton fraction; MPF_{Zsp}, MPF measured by the four-parameter fit of Z-spectroscopic images; MPF_{1pt}, MPF measured by the single-point method; MRI, magnetic resonance imaging; T, Tesla; 3D, three-dimensional; MT, magnetization transfer; MTR, MT ratio; MTsat, MT saturation; ihMTR, inhomogeneous MTR; PD, proton density; SNR, signal-to-noise ratio; RARE, rapid acquisition with relaxation enhancement; FSE, fast spin echo; GRE, gradient echo; TR, repetition time; TE, echo time; FOV, field of view; WM, white matter; GM, gray matter; VFA, variable flip angle; AFI, actual flip-angle imaging; ME, multi-echo; Δ, offset frequencies; ROI, region of interest; T_{1D}, dipolar order longitudinal relaxation time; T_2^F, T_2 of free protons; T_2^B, T_2 of bound protons; OB, olfactory bulbs; Cg, cingulum; CC, corpus callosum; CPu, caudate putamen; ECap, external capsule; ICap, internal capsule; F, fornix; SC, superior colliculus; IC, inferior colliculus; CWM, cerebellar white matter; CGM, cerebellar gray matter; Th, thalamus; H, hippocampus; Mc, motor cortex; Vc, visual cortex.

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more pronounced magnetic susceptibility artifacts, and changes in relaxation properties of tissues. A well-known problem in ultra-high-field MRI is a decrease of T_1-weighted tissue contrast with an increase of field strength (Balchandani and Naidich, 2015; de Graaf et al., 2006; van de Ven et al., 2007; Pohmann et al., 2011; Kara et al., 2013). For this reason, T_2-weighted imaging remains the only suitable modality for routine neuroanatomical applications in magnetic fields beyond 9–10 T. However, high-field T_2-weighted imaging has some limitations in the morphological context. T_2-weighted images are typically acquired using a sequence with multiple spin-echo readout (RARE or FSE). T_2 shortening in high fields precludes using large acceleration factors in this sequence due to degradation of image quality caused by point spread function broadening. In combination with a long repetition time (TR) required for T_2-weighting, 3D T_2-weighted imaging with sufficiently high resolution in all directions becomes prohibitively time-consuming for most small animal neuroimaging applications in vivo. Additionally, T_2-weighted imaging in high fields becomes very sensitive to the magnetic susceptibility effect caused by the presence of super-paramagnetic substances. This effect may result in obscuring anatomical details in cell labeling applications or in the presence of hemorrhage after surgical procedures. As such, small animal MRI in ultra-high magnetic fields is essentially lacking a technique that could afford high-resolution 3D visualization of brain morphology in vivo with minimal sensitivity to the susceptibility and paramagnetic effects and positive contrast between white matter (WM) and gray matter (GM).

One contrast mechanism that is potentially capable to mitigate contrast generation problems in ultra-high magnetic fields is the magnetization transfer (MT) effect. MT is frequently characterized by empirical semi-quantitative indexes describing changes in the signal intensity caused by radiofrequency saturation that is partially selective to the resonance of macromolecular protons. Examples of such indexes include MT ratio (MTR) (Dousset et al., 1992), MT saturation (MTsat) (Helms et al., 2008), and MTR difference observed in the recently proposed inhomogeneous MT experimental method (ihMTR) (Varma et al., 2015a). Some of these quantities, such as MTsat (Boretius et al., 2010) and ihMTR (Prevost et al., 2016) showed a promise in ultra-high field anatomical neuroimaging due to their capability to generate strong contrast between WM and GM on corresponding parametric maps. However, the above indexes are problematic to use for the objective quantitative characterization of pathological changes in tissues due to their complex dependence on the parameters of an imaging sequence and underlying biophysical model describing the MT effect. Alternatively, the MT effect can be characterized by a set of relaxation and cross-relaxation parameters defined within the two-pool model (Morrison and Henkelman, 1995). One parameter of this model describing a relative amount of immobile macromolecular protons involved into magnetization exchange with mobile water protons and termed below as the macromolecular proton fraction (MPF) is characterized by marked distinctions between WM and GM and strong associations with the myelin content established in a number of animal studies (Janve et al., 2013; Ou et al., 2009; Underhill et al., 2011; Samsonov et al., 2012; Thiessen et al., 2013). However, application of MPF maps for the purpose of structural neuroimaging is challenging, because their reconstruction typically involves multi-parameter fit procedures that require a large number of source images and are prone to substantial parameter uncertainties. This limitation has been overcome by the recent fast single-point MPF mapping method, which has enabled reconstruction of MPF maps in isolation from other two-pool model parameters based on a single MT-weighted image (Yarnykh, 2012; Yarnykh, 2016), thus facilitating clinically-targeted applications (Petrie et al., 2014; Yarnykh et al., 2015a; Yarnykh et al., 2015b). Latest human studies have demonstrated that MPF maps obtained using the single-point method are capable of generating very high contrast between WM and GM in the human brain at 3 T and provide clinically relevant information about demyelination in both WM and GM (Petrie et al., 2014; Yarnykh et al., 2015a; Yarnykh, 2016). Using the recently developed variant of fast MPF mapping (Yarnykh, 2016), which requires only three source images, 3D MPF maps can be obtained with high spatial resolution, whole-brain coverage, and clinically acceptable scan time. The main theoretical advantage of MPF as a quantitative MRI parameter is its independence of magnetic field strength. As such, one can expect that in high magnetic fields, MPF maps will provide not only a means for quantitative tissue characterization but also a useful modality for high-resolution neuroanatomical imaging.

While MPF itself is independent of magnetic field, such dependence may be expected for other parameters of the two-pool model. Since MPF measurements in the single-point method (Yarnykh, 2012) are based on constraining certain two-pool model parameters and their combinations, the corresponding constraints may be also field-dependent and need to be determined for specific field strengths. The objectives of this study were to characterize the two-pool model parameters in brain tissues in ultra-high magnetic fields and introduce fast high-field 3D MPF mapping as both anatomical and quantitative neuroimaging modality for small animal applications.

2. Materials and methods

2.1. Image acquisition

All described experiments have been carried out in accordance with the National Institutes of Health guide for the care and use of Laboratory animals. The experimental protocol was approved by the Bioethical Committee at the Institute of Cytology and Genetics (Siberian Branch, Russian Academy of Sciences). Four adult male Wistar rats were imaged under isoflurane anesthesia on a 11.7 T horizontal-bore animal MRI scanner (BioSpec 117/16 USR; Bruker BioSpin, Ettlingen, Germany) with a four-channel surface phased-array coil. To obtain maps of the two-pool model parameters, a series of brain MT-weighted images at a variable offset frequency (Δ) and effective flip angle (FA_{MT}) of the off-resonance saturation pulse (termed below Z-spectroscopic images) were acquired using a 3D MT-prepared spoiled gradient echo (GRE) sequence with TR/TE=25/2.7 ms and excitation flip angle $\alpha=9°$. For off-resonance saturation, Gaussian pulse was used with duration 10 ms, 12 Δ values in a range 0.75-48 kHz, and FA_{MT} = 500, 1000, and 1500°. Reference images for data normalization were acquired for each FA_{MT} at $\Delta=100$ kHz. Complementary $R_1=1/T_1$ maps were obtained using the variable flip angle (VFA) method with a 3D GRE sequence (TR/TE=25/2.7 ms, $\alpha=3$, 12, 20, 25, 30°). To correct for field heterogeneities, 3D B_0 and B_1 maps were acquired using the dual-TE ($TR/TE_1/TE_2$ = 20/2.9/5.8 ms, $\alpha=8°$) (Skinner and Glover, 1997) and actual flip-angle imaging (AFI) ($TR_1/TR_2/TE$ = 13/65/4 ms, $\alpha=60°$ (Yarnykh, 2007) methods, respectively.

All images were acquired in the axial plane with whole-brain coverage and resolution of 200x200 × 445 μm^3 (FOV = 34x30 × 16 mm, matrix size 170x150 × 36). Scan time for each Z-spectral and VFA data point was 1 min 41 s, and 1 min 48 s and 5 min 16 s for B_0 and B_1 mapping sequences, respectively Additionally, 2D T_2 mapping was performed with matched geometry and contiguous slices using multiple spin-echo sequence with TR=5 s and 16 echoes with 10 ms echo spacing (scan time 9 min 20 s).

To demonstrate the feasibility of high-resolution whole-brain MPF mapping, 3D MPF maps were obtained from three source images (MT-, PD-, and T1-weighted) with isotropic 170 μm^3