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High-resolution mechanical imaging of the human brain by three-dimensional multifrequency magnetic resonance elastography at 7T

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ABSTRACT

Magnetic resonance elastography (MRE) is capable of measuring the viscoelastic properties of brain tissue in vivo. However, MRE is still limited in providing high-resolution maps of mechanical constants. We therefore introduce 3D multifrequency MRE (3DMMRE) at 7T magnetic field strength combined with enhanced multifrequency dual elasto-visco (MDEV) inversion in order to achieve high-resolution elastographic maps of in vivo brain tissue with 1 mm^3 resolution. As demonstrated by phantom data, the new MDEV-inversion method provides two high resolution parameter maps of the magnitude ($|G^*|$) and the phase angle (ϕ) of the complex shear modulus. MDEV inversion applied to cerebral 7T-3DMMRE data of five healthy volunteers revealed structures of brain tissue in greater anatomical details than previous work. The viscoelastic properties of cortical gray matter (GM) and white matter (WM) could be differentiated by significantly lower values of $|G^*|$ and ϕ in GM (21% [$P < 0.01$]; 8%, [$P < 0.01$], respectively) suggesting that GM is significantly softer and less viscous than WM. In conclusion, 3DMMRE at ultrahigh magnetic fields and MDEV inversion open a new window into characterizing the mechanical structure of in vivo brain tissue and may aid the detection of various neurological disorders based on their effects to mechanical tissue properties.

Introduction

During the past few years, magnetic resonance imaging (MRI) at ultrahigh magnetic fields (UHF) of 7T and beyond has emerged as a promising imaging modality in neuroscience, providing images with better resolved anatomical details and improved signal-to-noise ratio (SNR) than conventional MRI (Duyn et al., 2007; Hu and Norris, 2004). The capability of 7T-MRI for high-resolution brain mapping has been exploited in a large variety of MRI methods such as susceptibility-weighted imaging (Deistung et al., 2008; Yao et al., 2009), diffusion-sensitive MRI (Heidemann et al., 2010; Reischauer et al., 2012), or functional MRI (Beisteiner et al., 2011; Poser and Norris, 2009; Wacker et al., 2011).

Magnetic resonance elastography (MRE) (Muthupillai and Ehman, 1996) is a special MRI-based technique which promises sensitivity to the microarchitecture of soft tissue due to the scaling properties of the shear modulus in biological systems (Posnansky et al., 2012). MRE was reported to be sensitive to subtle alterations of brain tissue associated with physiological aging (Sack et al., 2011), multiple sclerosis (Wuerfel et al., 2010), Alzheimer's disease (Murphy et al., 2012a), normal pressure hydrocephalus (Streitberger et al., 2011), and tumors (Murphy et al., 2012b). Micro-MRE in the mouse brain revealed marked softening of cerebral tissue related to demyelination, inflammation and neuronal loss (Freimann et al., 2013; Riek et al., 2012; Schregel et al., 2012). These results show that MRE provides additional information on pathologic processes that alter tissue integrity.

Previous technical developments of cerebral MRE relied either on 2D MRE with multifrequency excitation (MMRE) (Latta et al., 2011; Papazoglou et al., 2012; Sack et al., 2011; Streitberger et al., 2011) or on 3D MRE at a single driving frequency (Green et al., 2008; Hirsch et al., 2012; Johnson et al., 2013a,b; Murphy et al., 2011; Pattison et al.,

Abbreviations: EPI, echo planar imaging; GM, gray matter; GRAPPA, generalized autocalibrating partially parallel acquisitions; MDEV, multifrequency dual elastovisco (MDEV) inversion; MEG, motion-encoding gradient; MRE, magnetic resonance elastography; 3DMMRE, 3D MRE with multiple vibration frequency stimuli; FLASH, fast low-angle shot; FOV, field of view; UHF, ultrahigh magnetic field; ROI, region of interest; SNR, signal-to-noise ratio; WM, white matter.

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2010; Romano et al., 2012; Zhang et al., 2011). Only a few studies combined 3D MRE with multiple vibration frequency stimuli (3DMMRE) (Clayton et al., 2012).

Regardless of whether 2D or 3D methods are used, the MRE images obtained and the elastic parameter maps derived from these images have much lower resolution than anatomic MR images. Additionally, the computation of tissue mechanical parameters from shear waves needs to be revised, since the solution of the inverse problem in elastography is ill-posed and thus remains an obstacle to high-resolution MRE. The first issue, regarding image acquisition, has been tackled by using fast sequences based on spiral readout or echo-planar imaging (EPI), resulting in cerebral MRE wave images of $2 \times 2 \times 2$ mm^3 voxel size (Guo et al., 2013; Hirsch et al., 2012; Johnson et al., 2013b). The second issue, regarding wave mechanics, was addressed by multifrequency inversion of an overdetermined set of wave equations (Guo et al., 2013; Hirsch et al., 2013; Papazoglou et al., 2012) capable of compensating for destructive interferences regularly arising in single-frequency wave patterns.

This paper addresses both key issues, imaging physics and wave mechanics, by the use of 3DMMRE at 7T for high-resolution mapping of the mechanical parameters of brain tissue. In principle, ultrahigh magnetic fields increase the signal-to-noise ratio (SNR), which in turn can be exploited to increase the resolution. However, special challenges in UHF-MRI arise from several factors such as the reduced excitation wave lengths and shortened transverse relaxation times (T_2), imposing the need for shorter echo times (TE) (Hutton et al., 2011). For MRE (similar to diffusion imaging) this is a severe restriction as it limits the time for applying motion-encoding gradients and hence reduces motion sensitivity. Other challenges inherent to UHF-MRE arise from the narrow geometries of 7T-magnet bore and receive coils, which restrict the space available for the setup of mechanical actuators (Sack et al., 2008). On the other hand, one advantage is that electromechanical coil-based transducers produce high torque at ultrahigh magnetic fields and may thus serve as actuators for 7T brain MRE. A previous MRE study of the brain at 7T also showed that 2D MRE imaging is feasible but with a resolution comparable to that of standard 1.5T MRE examinations (Hamhaber et al., 2010).

This study is intended to exploit the advantages of 3DMMRE at UHF for high-resolution mechanical imaging of the human brain. We combine the high SNR and small voxel sizes achievable at 7T with multifrequency dual elastovisco (MDEV) inversion as recently introduced for 3DMMRE in the abdomen (Hirsch et al., 2013) and in the brain (Guo et al., 2013). Compared to our previous work, we here use a modified reconstruction algorithm which alleviates the effect of noise sensitive spatial derivatives in a least-squares solution of the Helmholtz equation and is thus potentially more robust against noise and discontinuities. This modified MDEV inversion will be further outlined in the Methods section and demonstrated with a phantom. To exploit the potential of the new method in the brain we will investigate the mechanical properties of the thin layer of cortical gray matter, which is below the resolution limits of classical MRE. Extrapolating the results of previous clinical studies with lower resolution (Murphy et al., 2012b; Streitberger et al., 2011; Wuerfel et al., 2010), we assume that a successful application of high-resolution MRE at ultrahigh fields will encourage further development of clinical applications such as early detection of small tumors or other early pathologic alterations of brain tissue.

Methods

Five healthy male volunteers (mean age, 40.4 ± 13.1 years) were examined. The study was conducted in accordance with the Human Subjects Guidelines of the Declaration of Helsinki and was approved by the Local Ethics Committee of our institution.

MR protocol

All experiments were carried out on a 7T MRI scanner (Siemens, Erlangen, Germany) using a 32-channel phased-array head coil (Nova Medical, Wilmington, MA, USA) in combination with a parallel imaging technique (GRAPPA, acceleration factor 3). After acquisition of a localizer (3 orthogonal slices of a standard FLASH sequence), a single-shot spin-echo echo-planar imaging (EPI) sequence with trapezoidal flow-compensated motion-encoding gradients (MEG), consecutively applied along all three axes of the scanner coordinate system, was used for rapid motion field acquisition in a slab of 20 contiguous slices of 1.0 mm^3 isotropic resolution.

A custom-made bite bar with attached electromagnetic coils was used to generate shear waves by inducing a tilted motion of the head. The vibration was triggered by the pulse sequence with a forerun of 100 ms to ensure that the waves propagated completely through the tissue before motion encoding was started. Fig. 1 shows the setup of the MRE experiment. One shear wave cycle was captured at eight time points by delaying the trigger pulse in increments of $1/(8f)$ with f being the vibration frequency. Vibration frequencies were 40, 50, and 60 Hz, and the MEG frequencies were set to 36, 44, and 71 Hz, respectively, with one gradient period for 36 and 44 Hz and two periods for 71 Hz. The MEG amplitude and slew rate were 50 mT/m and 100 mT/m/ms. For each vibration frequency, MEG direction, and time step, 20 transverse image slices were recorded in interleaved mode, yielding a total of 1440 images. For each image slice, the signal was averaged twice to improve SNR. The resulting total scan time was approximately 10 min for acquisition of a full 3DMMRE data set covering a volume of $20 \times 200 \times 186$ mm^3. Further imaging parameters were: repetition time (TR): 5640 ms; echo time (TE): 76 ms; and matrix size: 200×186.

Segmentation

To evaluate tissue viscoelasticity of gray matter (GM) and white matter (WM) tissue probability maps were generated using the SPM8 segmentation tool (Friston et al., 2007). A partial volume threshold of 0.7 and 0.8 was used to segment WM from GM, respectively.

Data processing

The data processing workflow is schematically shown in Fig. 2. Fig. 2a depicts exemplary phase data $\varphi_m(\mathbf{r}, t, \omega_n)$, which are wrapped ($\varphi_m \in [0, 2\pi)$). Here, $\mathbf{r}$ denotes the position vector, t the delay between MEG and the onset of vibration, ω_n the nth-angular drive frequency, and m the index of the wave component with $m = 1, 2$, and 3 referring to the imaging gradient directions of readout, phase-encoding, and slice-selection, respectively. For preprocessing, the phase data were unwrapped using Flynn's algorithm (Ghiglia and Pritt, 1998), scaled from radians φ_m to meter u_m by the factor given in Eq. (4b) of Hirsch et al. (2012), and then Fourier-transformed along the time axis. The resulting harmonic field was smoothed by a 3D Gaussian filter with a cubic convolution kernel of 3 pixels edge size.

To suppress compression waves, the curl components (Honarvar et al., 2013; Zhang et al., 2011) c_1^*, c_2^* and c_3^* were derived for each driving frequency from the corresponding complex wave images u_1^*, u_2^* and u_3^* as follows (asterisks denote complex quantities):

$$c_1^* = \frac{\partial u_3^*}{\partial x_2} - \frac{\partial u_2^*}{\partial x_3};\quad c_2^* = \frac{\partial u_1^*}{\partial x_3} - \frac{\partial u_3^*}{\partial x_1};\quad c_3^* = \frac{\partial u_2^*}{\partial x_1} - \frac{\partial u_1^*}{\partial x_2}. \tag{1}$$

These curl components were then low-pass-filtered to reduce noise by applying a 2D-Butterworth kernel with a threshold of 100 m^{-1}. The