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Characterization of normal appearing brain structures using high-resolution quantitative magnetization transfer steady-state free precession imaging

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ABSTRACT

Compared to standard spoiled gradient echo (SPGR)-methods, balanced steady-state free precession (bSSFP) provides quantitative magnetization transfer (qMT) images with increased resolution and high signal-to-noise ratio (SNR) in clinically feasible acquisition times. The aim of this study was to acquire 3D high-resolution qMT-data to create standardized qMT-values of many single brain structures that might serve as a baseline for the future characterization of pathologies of the brain.

QMT parameters, such as the fractional pool size (*F*), exchange rate (kf) and relaxation times of the free pool (T1, T2) were assessed in a total of 12 white matter (WM) and 11 grey matter (GM) structures in 12 healthy volunteers with MT-sensitized bSSFP. Our results were compared with qMT-data from previous studies obtained with SPGR-methods using MT-sensitizing preparation pulses with significantly lower resolution.

In general, qMT-values were in good accordance with prior studies. As expected, higher *F* and kf and lower relaxation times were observed in WM as compared to GM structures. However, many significant differences were observed within WM and GM regions and also between different regions of the same structure like in the internal capsule where the posterior limb showed significant higher kf than the anterior limb. Significant differences for all parameters were observed between subjects.

In contrast to previous studies, bSSFP allowed assessment of even small brain structures due to its high resolution. The observed differences from previous studies can partly be explained by the reduced partial volume effects.

MT-sensitized bSSFP is an ideal candidate for qMT-analysis in the clinical routine as it provides high-resolution 3D qMT-data of even small brain structures in clinically feasible acquisition times. The present qMT-data can serve as a reference for the characterization of cerebral diseases.

Introduction

Magnetization transfer (MT) is based on the exchange of spin magnetization between protons in free water ("liquid pool") and those bound to larger molecules ("semisolid or solid pool") (Cercignani et al., 2005; Henkelmann et al., 1993; Sled and Pike, 2001; Wolff and Balaban, 1989), thus providing information beyond conventional T1- and T2-Magnetic Resonance (MR) sequences. Although not belonging to the standard sequences in the daily clinical routine, studies characterizing the MT-effect in different pathologies, e.g. brain infarction, tumours and white matter (WM) lesions (Okumura et al., 1999; Fazekas et al., 2005; Ramani et al., 2002; Sled and Pike, 2001; Tozer et al., 2003) have been described.

In its simplest form of quantification, MT-effects are condensed into so-called magnetization transfer ratio (MTR) images being a rather qualitative measure for the quantity of bound protons present. Although MTR imaging is used in some centres in the clinical setting, it is difficult to be reproduced across different studies, as it highly depends on pulse sequence details and relaxation properties (Cercignani et al., 2005; Ou and Gochberg, 2008; Ramani et al., 2002; Tofts et al., 2003). Therefore, in characterizing the MT phenomenon by simply assessing MTR, potentially essential diagnostic information might be missed.

In contrast to MTR, quantitative MT (qMT) imaging provides information about the magnetization transfer rate (kf) between bound and free protons, and about the ratio (*F*) of the restricted pool size to the free pool size. In addition, qMT yields the T1- and T2-relaxation times (T1, T2) (Sled and Pike, 2001; Sled et al., 2004).

As qMT imaging (most commonly based on a two-pool MT model) reflects intrinsic tissue properties, it is believed to be more sensitive and specific to biological changes (Filippi, 1999; Ou and Gochberg, 2008; Ramani et al., 2002; Sled and Pike, 2001; Tofts et al., 2003; Tozer et al., 2003), and much less sensitive to sequence modifications (Ou and Gochberg, 2008; Sled et al., 2004; Yarnykh and Yuan, 2004).

So far, a number of imaging methods for qMT have been described in the literature that mainly differ in the state the magnetization is measured, that is: either in steady-state (Henkelmann et al., 1993;

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Ramani et al., 2002; Yarnykh, 2002; Yarnykh and Yuan, 2004) or during the transition to steady-state (Davies et al., 2004; Gochberg and Gore, 2007; Tozer et al., 2003; Wolff and Balaban, 1989). However, clinical application of these methods is mostly limited by either low signal-to-noise ratio (SNR), long acquisition times, limited resolution or limited brain coverage and/or only permit the assessment of a few of the various parameters that can be obtained by qMT imaging.

Only recently, a new MT-sensitized method, i.e. a fast imaging sequence based on balanced steady-state free precession (bSSFP) was proposed (Bieri and Scheffler, 2006, 2007), in which the addition of the MT-sensitizing off-resonance pulses prior to the proper MT measurement, indispensable in standard MT-spoiled gradient echo (SPGR) methods, is not needed. Here, qMT imaging is based on a modification of the duration and the excitation angle of the radio-frequency (RF) pulses used. In contrast to common qMT imaging, bSSFP is able to produce high-resolution whole brain qMT parameter maps with high SNR within 30 min, hereby promising to be a good candidate for qMT-analysis in the clinical routine.

For the establishment of a standardized high-resolution qMT reference data set for the interpretation of pathologies, normal appearing cerebral structures (12 WM and 11 grey matter (GM) structures) from 12 healthy volunteers were acquired with MT-sensitized bSSFP. Our results were compared with previously described qMT-data acquired with markedly lower spatial resolution.

Materials and methods

Image acquisition

All measurements were obtained at a 1.5 T MR whole body scanner (Avanto, Siemens Medical Solutions, Erlangen, Germany), equipped with a 12-channel head coil. Twelve healthy subjects (age range 26–45 years, 6 males and 6 females) underwent an imaging protocol including an axial unenhanced T1-weighted turbo spin echo (TSE) sequence, an axial T2-weighted TSE sequence, and an axial turbo inversion recovery magnitude (TIRM) sequence for anatomical exclusion of incidental findings, in addition to a sagittal 3D inversion recovery (IR) multi-planar magnetization prepared rapid acquisition gradient echo (MPRAGE) for anatomical reference. The MPRAGE acquisition and all qMT experiments were performed in 3D with a sagittal orientation based on a $144\times192\times192$ matrix and 1.3 mm isotropic resolution. QMT imaging included a multislice (16 slices, 5 mm slice thickness) B1 map (64×64 matrix, 4 mm in plane resolution) based on a stimulated echo sequence, two RF spoiled gradient echo (GRE) sequences with variable flip angles of $\alpha=4°$ and $\alpha=15°$ (TR/TE = 9.8 ms/4.77 ms) for T1 mapping according to DESPOT1 (Homer and Roberts, 1987; Deoni et al., 2005), and 16 bSSFP sequences using 8 different RF pulse durations ($T_{RF}=230$ µs–2100 µs, $\alpha=35°$) and 8 different flip angles ($\alpha=5°$–$40°$, TR/T_{RF} = 2.99 ms/0.27 ms). Off-resonance related artifacts were reduced by manual shimming within the brain. Acquisition parameters are found in more detail elsewhere (Gloor et al., 2008). The qMT protocol was completed within 30 min.

Image post-processing

Brain registration and segmentation were done with the software packages FSL (Smith et al., 2004) and AFNI (Cox, 1996). Flip angle correction based on the B1 field map, T1 determination based on the RF spoiled GRE sequences and pixel-by-pixel non-linear least-squares fitting of the parameters *F*, kf and T2 from the 16 bSSFP acquisitions were performed using Matlab 2006a (The MathWorks, Inc., Natick, MA). Theoretical derivation of the underlying equations is given elsewhere (Gloor et al., 2008). Twelve WM and eleven GM structures were identified and corresponding masks were drawn by an experienced radiologist, covering: (i) deep WM and cortical GM bilaterally for all four lobes (frontal, temporal, parietal, occipital), (ii) the head of the caudate nucleus, the putamen, the globus pallidus, the thalamus, the mamillary body, the amygdala, the hippocampus, the crus cerebri, and the anterior and posterior limb of the internal capsule (IC) bilaterally, and as midline structures (iii) the anterior commissure and the four different parts of the corpus callosum (CC) (rostrum, genu, body and splenium). For the frontal, temporal and occipital lobes, masks were created at the transition from the superior to the medial gyrus and sulcus, whereas the masks for the parietal lobe were drawn at the transition from the parietal lobulus to the angular gyrus. The lateral borders of the cortical GM masks were omitted to avoid inclusion of extracerebral or adjacent WM tissue. For all other cerebral structures, masks were slightly reduced by their anatomical margins to avoid partial volume effects from adjacent tissue or cerebral spinal fluid. All masks were drawn for each subject individually using FSL (FSL, Oxford, UK, www.fmrib.ox.ac.uk/fsl), and were of approximately the same size for all subjects. Special care was taken to draw the bilateral masks as symmetrically as possible in both hemispheres within the same as well as between all subjects. All masks were reviewed by a second experienced radiologist for proper anatomical localization and size. Examples of masked WM and GM structures are presented in Fig. 1.

Application of masks on qMT-data was performed using Matlab (The MathWorks, Inc., Natick, MA, USA), yielding the quantitative two-pool MT model parameters *F* and kf, as well as the free pool relaxation times T1 and T2 (Fig. 2). In addition, mean values for WM, GM, IC and CC (calculated as the mean values of all contributing structures) are given in Table 1.

Statistical analysis

For statistical analysis of results, two series of a two-way analysis of variances (ANOVA) factored into side of hemisphere (right/left) and structures (first series) and into structures and subjects (second series) were performed for each parameter (*F*, kf, T1, T2) and type of tissue (WM and GM). A *p*-value of less than 1% was considered to be statistically significant.

For testing for differences between male and female patients for all parameters and for all structures, the Mann–Whitney *U* test was used, as

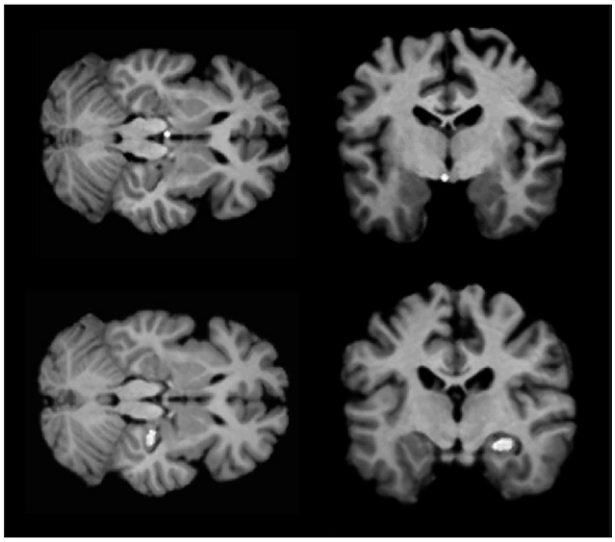

Fig. 1. Axial (left) and coronal (right) images showing masks located in the left mamillary body (upper row) and right hippocampus (lower row).