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Comparison between balanced steady-state free precession and standard spoiled gradient echo magnetization transfer ratio imaging in multiple sclerosis: methodical and clinical considerations

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ABSTRACT

Different pathological processes like demyelination and axonal loss can alter the magnetisation transfer ratio (MTR) in brain tissue. The standard method to measure this effect is to scan the respective tissue twice, one with and one without a specific saturation pulse. A major drawback of this technique based on spoiled gradient echo (GRE) sequences relates to its long acquisition time due to the saturation pulses. Recently, an alternative concept for MT imaging based on balanced steady state free precession (bSSFP) has been proposed. Modification of the duration of the radiofrequency pulses for imaging allows scanning MT sensitive and non-sensitive images. The steady-state character of bSSFP with high intrinsic signal-to-noise ratio (SNR) allows three-dimensional (3D) whole brain MTR at high spatial resolution within short and thus clinically feasible acquisition times. In the present study, both bSSFP-MT and 2D GRE-MT imaging were used in a cohort of 31 patients with multiple sclerosis (MS) to characterize different normal appearing (NA) and pathological brain structures. Under the constraint of identical SNR and scan time, a 3.4 times higher voxel size could be achieved with bSSFP. This increased resolution allowed a more accurate delineation of the different brain structures, especially of cortex, hippocampus and MS lesions. In a multiple linear regression model, we found an association between MTR of cortical lesions and a clinical measure of disability ($r = -0.407$, $p = 0.035$) in the bSSFP dataset only. The different relaxation weighting of the base images (T2/T1 in bSSFP, proton density in GRE) had no effects besides a larger spreading of the MTR values of the different NA structures. This was demonstrated by the nearly perfect linearity between the NA matter MTR of both techniques as well as in the absolute MTR differences between NA matter and the respective lesions.

Introduction

The effect of magnetization transfer (MT) was first described in 1989 by Wolff and Balaban (Wolff and Balaban, 1989). Physically, MT refers to the exchange of magnetization between protons of a highly mobile phase associated with bulk free water and protons of a rather "rigid" macromolecular phase associated with protein matrices or cell membranes. This exchange can be altered by pathological processes like edema and inflammation (Dousset et al., 1992; van Buchem et al., 1997) but especially by demyelination and axonal loss (Dousset et al., 1992). These alternations in magnetization exchange are most commonly assessed in terms of MT ratio (MTR). The standard method to measure MTR is to scan the respective tissue twice, once with and once without a specific MT saturation pre-pulse (Barker et al., 2005; Cercignani et al., 2005; Dousset et al., 1992). A major drawback of this technique based on spoiled gradient echo (GRE) sequences is its long acquisition time due to the application of the saturation pulses. In addition, GRE-MT imaging suffers from limited reproducibility across different studies and across different centers as it is very sensitive to the exact parameters of the pulse sequence, and especially to B1 field calibration and homogeneity (Barker et al., 2005; Ropele et al., 2005).

Recently, an alternative and fast concept for MT imaging, based on balanced steady state free precession (bSSFP) has been proposed (Bieri and Scheffler, 2006, 2007). Modification of the duration of the radiofrequency (RF) pulses used for imaging makes it possible to scan MT sensitive and non-sensitive images (Bieri and Scheffler, 2007). The

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steady-state character of bSSFP with high intrinsic signal-to-noise ratio (SNR) allows three-dimensional (3D) whole brain MTR at high spatial resolution within short and thus clinically feasible acquisition times.

Since the discovery of the intrinsic MT effect of bSSFP, MT-sensitized 3D bSSFP was evaluated in several small studies. For example, it was used to quantify MTR of healthy brain structures in adults (Garcia et al., 2011). Two dimensional cine variants of bSSFP were used in studies measuring MTR of cardiac tissue in healthy controls and in patients with acute myocardial infarcts (Weber et al., 2009) and in an animal model where the MT effect additionally enhanced the contrast between healthy myocardium and oedema (Zhou et al., 2011). Beyond simple MTR measurements, the overall MT sensitivity of bSSFP in combination with its high SNR and the short acquisition time allows measuring quantitative MT (qMT) in a clinical setup (Gloor et al., 2008). QMT imaging was applied to characterize healthy brain structures (Garcia et al., 2010) and to link the quantitative measures (fraction of restricted pool protons, corresponding magnetization exchange rates, and relaxation times) to the semi-quantitative MTR (Garcia et al., 2012).

Using standard MTR techniques, it has been shown that MTR of brain tissue is reduced (Grossman, 1994) even at very early stages of multiple sclerosis (MS) (Crespy et al., 2011; Davies et al., 2005), which is an inflammatory-demyelinating disease of the central nervous system. Additionally, MTR seems to correlate well with the degree of myelin loss (Schmierer et al., 2004) and more generally with tissue destruction (Dousset et al., 1992; van Waesberghe et al., 1999). Therefore, MS seems to be a particularly suitable model to test for disease-induced changes of MTR and the sensitivity of different MTR techniques.

Advantages and disadvantages of brain imaging with the bSSFP-MT technique have not been systematically compared to standard GRE-MT in larger clinical study populations. In the present study, both techniques were used to study 31 patients with MS to characterize tissue properties of different normal appearing and pathological brain structures. With bSSFP, a 3.4 times higher voxel size compared to GRE-MT can be achieved under the constraint of identical signal-to-noise ratio (SNR) and scan time. We therefore analysed the effects of this increased spatial resolution, as well as the effects based on the different relaxation weighting of both MT techniques.

Materials and methods

Subjects

Thirty-one MS patients (19 women, 12 men) with a relapsing-remitting disease course participating in an ongoing cohort study on MS were included in this MTR project. Data acquisition took place during a period of nine months in these patients. They underwent a detailed clinical neurological assessment including Expanded Disability Status Scale (EDSS) scoring by an EDSS certified neurologist (http://www.neurostatus.net). The patients were treated according to best practice at the discretion of the treating neurologist with disease modifying treatments at the time of the MRI and were clinically stable. Patients with an acute relapse were not examined and the MRI scan was postponed at least 30 days after the last dose of steroid treatment. Written informed consent was obtained from all participating patients in accordance with the local ethics committee approval. Mean age of the patients was 54.4 years (range 32–72 y), mean disease duration from first clinical symptoms was 20.8 years (range 4–48 y), and median EDSS was 3.0 (range 0.0–7.0), indicating moderate physical disability.

MRI

All measurements were performed on a 1.5 Tesla scanner (Magnetom Avanto, Siemens Medical, Erlangen, Germany) using the manufacturer's 12-element head matrix coil. In our institution, a multi-slice two-dimensional (2D) GRE sequence is used as the standard sequence for measuring MTR (GRE-MTR). The parameters of this sequence were: repetition time (TR) of 1180 ms, echo time (TE) of 12 ms and flip angle (α) of 25°. The MT saturation pulse has an offset frequency of 1.2 kHz, a Gaussian envelope duration of 9.98 ms and an effective flip angle of 500°. Forty slices were acquired in axial orientation parallel to the inferior borders of the corpus callosum. The voxel size of the GRE-MT was 1×2 mm^2 (interpolated to 1x1 mm^2) with a slice thickness of 4 mm. With these sequence parameters, the acquisition time was 4:36 min for both scans with and without saturation pulse.

In initial pilot measurements in healthy volunteers, the sequence parameters of the 3D bSSFP-MT technique were adapted to yield similar scan times, signal-to-noise ratio (SNR) and MTR values of NA white matter (WM) compared to the standard GRE-MT sequence. Under these constraints, the voxel size for the 3D bSSFP was $1.3\times1.3\times1.3$ mm^3 with a scan time (two acquisitions, parallel imaging with acceleration factor 2) of 4:42 min (again for both scans). One hundred forty-four partitions were acquired in sagittal orientation parallel to the inter-hemispheric fissure. The flip angle α was chosen to be 35°, gaining maximal MT effects and minimal B1 field sensitivity (Gloor et al., 2011). The RF pulse duration (TRF) of the MT sensitized acquisition was 0.08 ms (TR = 2.67 ms); TRF of the non-MT sensitized acquisition was 1.2 ms (TR = 3.79 ms), TE was 1.34 ms. With the chosen TRF, the MTR values for NAWM were similar in both bSSFP and GRE.

The study protocol also encompassed a 3D double inversion recovery (DIR) sequence (TR/inversion times (TI1, TI2)/TE = 7.5 s/450 ms/3.0 s/307 ms; voxel size $1.3\times1.3\times1.5$ mm^3) for the delineation of white matter and grey matter MS lesions (Geurts et al., 2005). The non-selective DIR was based on the SPACE technique (Sampling Perfection with Application optimized Contrasts using different flip angle Evolutions).

A 3D T1 weighted sequence (MPRAGE, TR/TI/TE/α = 2080 ms/1100 ms/3.93 ms/15°; $1\times1\times1$ mm^3) was scanned for the purpose of tissue segmentation. The entire scanning protocol lasted 26 minutes. All 3D sequences were acquired in sagittal orientation parallel to the inter-hemispheric fissure.

Data evaluation

Post-processing of the imaging data was performed with FSL (Smith et al., 2004), AFNI (Cox, 1996), and Matlab (http://www.mathworks.com).

For both MT techniques, the MT sensitized data sets were realigned to the non-MT sensitized data sets using FLIRT (Jenkinson et al., 2002) and MTR maps were calculated according to Eq. (1), given in percent units:

$$MTR = \frac{S_0 - S_{MT}}{S_0} \cdot 100\% \quad (1)$$

where S_0 refers to the signal of the non-MT-sensitized image, and S_{MT} refers to the signal of the MT-sensitized image.

The 3D T1-weighted volumes were segmented into grey matter (GM), WM and cerebrospinal fluid with FAST (Zhang et al., 2001), subcortical segmentation was performed using FIRST (Patenaude et al., 2011). The segmentation masks of the deep grey matter structures were visually inspected and falsely classified voxels were corrected manually by an experienced rater. The following subcortical structures were segmented: nucleus accumbens (Acc), amygdala (Amy), caudate nucleus (Cau), pallidum (Pal), putamen (Put), and thalamus (Tha). Additionally, the hippocampus (Hipp) was also segmented. The subcortical structures were subtracted from the masks obtained from FAST to get pure WM and pure cortex masks. In addition, the masks of Acc, Cau, Pal, and Put were combined to obtain a basal ganglia (BG) mask.

MS lesions were outlined on the DIR images using the semi-automatic contour software AMIRA 3.1.1 (Visage Imaging Inc., San Diego, CA). All lesions were classified as either cortical/mixed cortical-WM lesions, pure white matter lesions (WML) or pure deep grey matter