NeuroImage 179 (2018) 144–155

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Chemical exchange saturation transfer MRI contrast in the human brain at 9.4 T

Moritz Zaiss [a,*], Mark Schuppert [a], Anagha Deshmane [a], Kai Herz [a], Philipp Ehses [b], Lars Füllbier [c], Tobias Lindig [d], Benjamin Bender [d], Ulrike Ernemann [d], Klaus Scheffler [a,e]

[a] High-field Magnetic Resonance Center, Max Planck Institute for Biological Cybernetics, Tübingen, Germany
[b] German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany
[c] Department of Neurosurgery, Eberhard-Karls-University Tübingen, Tübingen, Germany
[d] Department of Diagnostic and Interventional Neuroradiology, Eberhard-Karls University Tübingen, Tübingen, Germany
[e] Department of Biomedical Magnetic Resonance, Eberhard-Karls University Tübingen, Tübingen, Germany

ARTICLE INFO

Keywords:
Chemical exchange saturation transfer
9.4 T
Ultra-high field
Human brain
APT
NOE

ABSTRACT

Purpose: The high chemical shift separation at 9.4 T allows for selective saturation of proton pools in exchange with water protons. For the first time, highly selective and comprehensive chemical exchange saturation transfer (CEST) experiments were performed in the human brain at 9.4 T. This work provides insight into CEST signals in the human brain in comparison with existing animal studies, as well as with CEST effects in vivo at lower field strengths.

Methods: A novel snapshot-CEST method for human brain scans at 9.4 T was optimized and employed for highly-spectrally-resolved (95 offsets) CEST measurements in healthy subjects and one brain tumor patient. Reproducibility and stability between scans was verified in grey and white matter after B_0, B_1, and motion correction of the acquired 3D CEST volumes. Two-step Lorentzian fitting was used to further improve separation of spectrally discernible signals to create known and novel CEST contrast maps at 9.4 T.

Results: At a saturation power of $B_1 = 0.5\,\mu T$ most selective CEST effects could be obtained in the human brain with high inter-scan reproducibility. While contrast behavior of previously measured signals at lower field, namely amide-, guanidyl- and NOE-CEST effects, could be reproduced, novel signals at 2.7 ppm, and −1.6 ppm could be verified in healthy subjects and in a brain tumor patient for the first time.

Conclusion: High spectral resolution chemical exchange saturation transfer at 9.4 T allows deeper insights into the Z-spectrum structure of the human brain, and provides many different contrasts showing different correlations in healthy tissue and in tumor-affected areas of the brain, generating hypotheses for future investigations of in-vivo-CEST at UHF.

Introduction

Chemical exchange saturation transfer (CEST) allows for indirect detection of diluted molecules via their saturation transfer to the abundant water pool (Forsen and Hoffman, 1963; Ward et al., 2000; Zhou et al., 2003). Separated by their individual chemical shift, several different diluted solutes were reported to be detectable using CEST such as peptides and proteins (Zhou et al., 2003; Jones et al., 2013; Zaiss et al., 2013, 2015, 2017a; Goerke et al., 2015, 2017), creatine (Kogan et al., 2014; Rerich et al., 2015), glutamate (Cai et al., 2012; Haris et al., 2013), as well as injected solutes such as iopamidol (Aime et al., 2005; Longo et al., 2013; Jones et al., 2015), glucose (Chan et al., 2012; Walker-Samuel et al., 2013; Xu et al., 2015; Schuenke et al., 2017a) and glucose derivatives (Nasrallah et al., 2013; Rivlin et al., 2014). This variety of detectable signals is owed to the chemical shift separation, which increases with the static field strength. Actually, at ultra-high fields (UHF), not only is the separation of CEST peaks easier, but also effect strength can be increased, as shown for amide, amine and NOE CEST effects (Chung et al., 2017), for hydroxyl protons close to water, as found in glycosaminoglycans in cartilage (Singh et al., 2012), as well as for the exogenous agent iopamidol (Longo et al., 2009). In addition to the increased frequency separation and higher CEST effect strengths, higher

* Corresponding author. High-field Magnetic Resonance Center, Max Planck Institute for Biological Cybernetics, Max-Planck-Ring 11, Tübingen, Germany.
E-mail address: moritz.zaiss@tuebingen.mpg.de (M. Zaiss).

https://doi.org/10.1016/j.neuroimage.2018.06.026
Received 8 February 2018; Received in revised form 7 June 2018; Accepted 8 June 2018
Available online 15 June 2018

List of abbreviations

APT	amide proton transfer
A_{ssMT}	amplitude of the Lorentzian function fitting the semi-solid MT pool at around −1.5 ppm
CEST	chemical exchange saturation transfer
FLAIR	fluid attenuation inversion recovery
GRE	gradient-echo
MT, ssMT	semi-solid magnetization transfer
NOE	nuclear Overhauser effect
T_1	longitudinal relaxation time
T_{1ce}	T_1 contrast enhanced
T_{1w}	T_1 weighted
T_2	transversal relaxation time
T_{2w}	T_2 weighted
TA	acquisition time (per offset)
T_{sat}	total saturation time, duration of saturation pulse train

static fields strengths also provide an over-proportional SNR gain (Pohmann et al., 2016), which makes detection of small CEST effects more reliable. Several studies could already detect CEST effects at 9.4 T in animals, showing high-spectral-resolution Z-spectra and novel CEST peaks at $\Delta\omega = +2.0$ ppm (Cai et al., 2015; Zhang et al., 2017a; Chen et al., 2017) associated with creatine and proteins, and $\Delta\omega = -1.6$ ppm, tentatively associated with choline phospholipids (Zhang et al., 2016). Thus, the investigation of these signals in the human brain will allow judgement whether animal findings are translatable to humans, and extend previous 7 T studies.

In previous work, feasibility of CEST MRI at 9.4 T of the human brain was demonstrated with high quality, and within SAR and RF amplifier limits (Zaiss et al., 2017b). The present work utilizes this methodology and provides a detailed analysis of Z-spectra of the human brain in vivo at $B_0 = 9.4$ T. Our goal is to identify optimized parameters for high-resolution CEST MRI at 9.4 T and provide a comprehensive analysis of CEST contrast at 9.4 T in the healthy human brain as well as a tumor patient.

After optimization of saturation power B_1, saturation time, and validation of reproducibility, it is shown that APT, NOE and guanidyl CEST effects can be detected robustly, and that at 9.4 T, using high irradiation frequency offset sampling also reveals peaks at $\Delta\omega = +2.7$ ppm, $\Delta\omega = -1.6$ ppm for the first time in the human brain. In addition to removal of direct water saturation and semi-solid MT background, as previously shown at 7 T (Zaiss et al., 2015), a subsequent multi-Lorentzian fit is introduced which enables mapping of individual peak amplitudes. While the sizes of these individual effects are investigated in detail in healthy subjects, preliminary data of a brain tumor patient study reveals that the isolated peaks also show different behavior in brain tumor areas.

Methods

MR imaging

Imaging was performed on a 9.4 T whole body MRI system (Siemens Healthcare, Erlangen, Germany) on 4 healthy subjects and on one patient with a brain tumor (histopathologically proven Glioblastoma WHO Grade IV, molecular profile: IDH1/2 wild type, MGMT-promoter methylated, ATRX retained), with informed consent provided prior to the MRI experiments and approval by the local ethics committee. A custom-built head coil was used for signal transmission/reception (16 Tx/31 Rx channels) (Shajan et al., 2014). The optimized 3D snapshot-CEST (Zaiss et al., 2017b) acquisition consists of a presaturation module of 4.5 s followed by a readout module of duration $T_{RO} = 2.5$ s, in which a train of RF and gradient spoiled gradient echoes with centric spiral reordering was acquired. Imaging parameters were FOV = 220 × 180 × 32 mm^3, matrix size 144, 80% FOV in the first phase-encoding direction; TE = 1.85 ms, TR = 3.64 ms, BW = 700 Hz/px, 18 slices, FA = 5° and elongation factor E = 0.6 (rectangular spiral reordered).

The spectrally but not spatially selective CEST saturation period consists of a train of 150 Gaussian-shaped RF pulses, using a pulse duration of $t_{pulse} = 15$ ms separated by a pulse delay of $t_{delay} = 15$ ms, resulting in a total saturation time of $T_{sat} = 4.5$ s, and nominal B_1 values of $B_1 = 0.6$ μT, 0.9 μT, 1.2 μT. After the pulse train, a crusher gradient was applied to spoil residual transversal magnetization. Z-spectrum data was obtained after saturation at 95 offsets in the range of ±50 ppm with denser sampling in the range of ±5 ppm (Zaiss et al., 2017b). Z-spectra were normalized by M_0 scans with 12 s of relaxation and saturation at $\Delta\omega = -300$ ppm. After each acquisition a recovery time of $T_{rec} = 1.1$ s takes place. Acquisition time per offset was $TA = T_{rec} + T_{sat} + T_{RO} = 8.1$ s. For 95 offsets, this yields a total scan time of approximately $TA_{tot} = 12$ min for one high-resolution CEST-spectrum scan. For CEST at three different B_1 levels, B_0 and B_1 mapping using WASABI (Schuenke et al., 2017b), and T_1 mapping using a saturation recovery sequence, the total examination time of the highly-resolved CEST protocol was 40 min. During the patient scan, the CEST images were acquired at only two B_1 levels due to limited scan time ($B_1 = 0.9$ μT, and 1.2 μT).

Grey matter (GM) and white matter (WM) regions for region-of-interest (ROI) evaluation were defined based on the T_1 map acquired by a saturation recovery sequence using 3 adiabatic half-passage pulses with subsequent crusher gradients for saturation and 14 different recovery times between 0.1 s and 10 s acquired with the same snapshot readout.

For ROI definition of tumor areas, the following co-registered clinical contrasts measured at $B_0 = 3$ T were used: gadolinium contrast enhanced T_1 (tumor ring enhancement, necrosis), T_{2w} (grey and white matter), and FLAIR (edema). For ROI drawing and direct comparison, the T_1-weighted contrast enhanced 3 T image (T_{1ce}) was co-registered to a T_1-weighted image of the saturation recovery measurement at 9.4 T; the resulting transformation was applied to all other 3 T contrasts.

Data evaluation

A flow chart of the data evaluation pipeline can be found in the supporting information Fig. S0. Z-spectrum data was first corrected for motion using AFNI's 3Dvolreg function (Cox and Hyde, 1997), followed by B_0 and B_1 inhomogeneity correction using the WASABI approach (Schuenke et al., 2017b), and the Z-3-point-B_1-correction method (Windschuh et al., 2015) (images reconstructed at $B_1 = 0.5$ μT). Reference images are then manually masked to isolate CSF, GM and WM. CEST images were generated from the Z-value Z (Δω), given by the ratio of the saturated image S_{sat} (Δω) and the fully relaxed image S_0

$$Z(\Delta\omega) = \frac{S_{sat}(\Delta\omega)}{S_0} \quad (1)$$

The magnitude of CEST effects is described by the magnetization transfer ratio (MTR). To isolate CEST effects from direct water saturation (spillover) and semi-solid magnetization transfer (ssMT), the Lorentzian difference (MTR_{LD}) method was used according to (Zaiss et al., 2015):

$$MTR_{LD}(\Delta\omega) = Z_{fit,water,MT}(\Delta\omega) - Z(\Delta\omega) \quad (2)$$

The starting values and boundary conditions for this two-pool Lorentzian fit are given in the Supporting information Table S1.

Individual CEST effects were subsequently isolated by applying a five-pool multi Lorentzian fit on the MTR_{LD}-spectra f (Δω):

$$f(\Delta\omega) = c + L_{3.5} + L_{2.7} + L_{2.0} + L_{-1.6} + L_{-3.5} \quad (3)$$

Each Lorentzian function L_x was defined as