NeuroImage 147 (2017) 619–631

Contents lists available at ScienceDirect

NeuroImage

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

The γ-parameter of anomalous diffusion quantified in human brain by MRI depends on local magnetic susceptibility differences

A. Caporale[a,b,*], M. Palombo[b,c], E. Macaluso[d], M. Guerreri[b,e], M. Bozzali[f], S. Capuani[b]

[a] Morpho-functional Sciences, Department of Anatomical, Histological, Forensic and of the Locomotor System Science, Sapienza University of Rome, Italy
[b] CNR ISC UOS Roma Sapienza, Physics Department Sapienza University of Rome, Rome, Italy
[c] MIRCen, CEA/DSV/I^{2}BM, Fontenay-aux-Roses, France
[d] ImpAct Team, Lyon Neuroscience Research Center, Lyon, France
[e] Morphogenesis & Tissue Engineering, Department of Anatomical, Histological, Forensic and of the Locomotor System Science, Sapienza University of Rome, Italy
[f] Neuroimaging Laboratory Santa Lucia Foundation, Rome, Italy

ARTICLE INFO

Keywords:
Anomalous diffusion imaging
R_2*
Magnetic susceptibility difference
DTI
Iron

ABSTRACT

Motivated by previous results obtained in vitro, we investigated the dependence of the anomalous diffusion (AD) MRI technique on local magnetic susceptibility differences (Δχ) driven by magnetic field inhomogeneity in human brains. The AD-imaging contrast investigated here is quantified by the stretched-exponential parameter γ, extracted from diffusion weighted (DW) data collected by varying diffusion gradient strengths. We performed T_2* and DW experiments in eight healthy subjects at 3.0 T. T_2*-weighted images at different TEs=(10,20,35,55) ms and DW-EPI images with fourteen b-values from 0 to 5000 s/mm^2 were acquired. AD-metrics and Diffusion Tensor Imaging (DTI) parameters were compared and correlated to R_2* and to Δχ values taken from literature for the gray (GM) and the white (WM) matter. Pearson's correlation test and Analysis of Variance with Bonferroni post-hoc test were used. Significant strong linear correlations were found between AD γ-metrics and R_2* in both GM and WM of the human brain, but not between DTI-metrics and R_2*. Depending on Δχ driven magnetic field inhomogeneity, the new contrast provided by AD-γ imaging reflects Δχ due to differences in myelin orientation and iron content within selected regions in the WM and GM, respectively. This feature of the AD-γ imaging due to the fact that γ is quantified by using MRI, may be an alternative strategy to investigate, at high magnetic fields, microstructural changes in myelin, and alterations due to iron accumulation. Possible clinical applications might be in the field of neurodegenerative diseases.

1. Introduction

Within the past few years there has been much effort to improve Magnetic Resonance imaging (MRI) techniques to provide susceptibility maps, such as gradient echo (GRE) phase imaging (Rauscher et al., 2005), Susceptibility Weighted-Imaging (SWI) (Haacke et al., 2004), Quantitative Susceptibility Mapping (QSM) (Duyn et al., 2007) and Susceptibility Tensor Imaging (STI) (Liu, 2010). Indeed, quantifying susceptibility is profitable because its variations are related to abnormally increased iron concentrations that characterize some neurological diseases such as Parkinson's disease (Zecca et al., 2004), Alzheimer's disease (Todorich and Connor, 2004), Multiple Sclerosis (Schmierer et al., 2010), and other disabling disorders such as migraine and chronic daily headache (Tepper et al., 2012). On the other hand, the evaluation of iron content in vivo is a practical problem that has not a reliable and sensitive method to be solved, despite the efforts done so far (Bartzokis et al., 1997, 2007; Pfefferbaum et al., 2010). Moreover, the quantification of magnetic susceptibility differences (Δχ) at the interface between neighbouring tissues could be of great help for highlighting tissues oriented along different directions compared to the main magnetic field (Chen et al., 2013). In this regard, STI quantifies the amount of magnetic susceptibility anisotropy, which is due to the micro-architecture and chemical arrangement of the neural tissue being probed (Lee et al., 2010; Liu, 2010). However, in order to compute the susceptibility tensor it is necessary to acquire the signal along at least six different orientations of the sample with respect to the static magnetic field $\mathbf{B_0}$ (Liu, 2010). This represents an intrinsic limitation of STI imaging, since the sample rotation is hardly practicable in the case of clinical applications in humans.

Abbreviations: AD, Anomalous Diffusion; DW, Diffusion Weighted; GM, Gray Matter; ROI, Region Of Interest; SD, Standard Deviation; SEM, Standard Error of the Mean; T2*WIs, T2* Weighted Images; VOI, Volume Of Interest; WM, White Matter

* Corresponding author at: CNR ISC UOS Roma Sapienza, Physics Department, Sapienza University of Rome, Piazzale Aldo Moro, 5, 00185, Rome, Italy.
E-mail address: alessandra.stella.caporale@gmail.com (A. Caporale).

http://dx.doi.org/10.1016/j.neuroimage.2016.12.051
Received 11 July 2016; Accepted 19 December 2016
Available online 21 December 2016
1053-8119/

In anomalous diffusion (AD) models, γ-maps representative of the stretching parameter γ derived from fitting a stretched function $S(b)=S(0)\exp(-(bD)^{\gamma})$ to diffusion weighted (DW) data, provide an interesting and novel source of contrast in MRI (Magin et al., 2008; De Santis et al., 2011; Hall and Barrick, 2012; Ingo et al., 2014). By using a tensor representation of AD, scalar invariant indices such as the mean γ (Mγ) and the γ anisotropy (Aγ) can be quantified in cerebral tissues (De Santis et al., 2011). In particular, the AD contrast obtained by using DW data acquired as a function of b-values and collected by changing diffusion gradient (g_{diff}) strength at a constant value of Δ is due to intravoxel diffusion heterogeneity in space. Specifically, water molecules diffuse with considerably different free lengths, and this mechanism is quantified by the stretched exponential parameter γ. Some authors indicate this peculiar AD mechanism as 'water jumping', formally derived in the space fractional derivatives approach (Magin et al., 2008; Ingo et al., 2014); other authors refer to this mechanism with the expression 'pseudo-superdiffusion' processes (Palombo et al., 2011, 2012; Capuani et al., 2013) due to both water multi-compartmentalization and Δχ at the interface between different compartments (Palombo et al., 2012). In vitro studies performed by Capuani et al. on phantoms with capillaries filled with polystyrene micro-beads dispersed in water (Palombo et al., 2011, 2012; Capuani et al., 2013) showed a strong inverse correlation between measured internal gradients (G_{int}) generated by Δχ and the γ parameter. This strong correlation can be explained considering the coupling between diffusion gradients (g_{diff}) and G_{int} which causes an irreversible DW signal loss that can be modeled as a pseudo-superdiffusion process. Specifically, local gradients induce a phase shift to the spins within a space region strictly close to the interfaces, which adds up to the phase shift given by the g_{diff} pulse, namely originating an effective gradient $\mathbf{G_{eff}=G_{int}+g_{diff}}$. When G_{int} and g_{diff} are in the same order of magnitude, some spins contribute to increase the DW signal attenuation; other spins (that can be located far from the first ones) acquire a phase that will help to increase the signal. Due to indistinguishable spins associated with water molecules, this scenario mimics a super-diffusion regime. The water signal disappears in one spot and appears in another one, thus simulating long jumps of water molecules.

In γ-MRI the water diffusion is analyzed by means of the AD-model, and this contrast mechanism seems to increase the sensitivity of the technique to tissue interfaces. This suggests a dependence of the signal of diffusing spins on local magnetic inhomogeneities (Palombo et al., 2012; Capuani et al., 2013). Magnetic inhomogeneities can be quantified by G_{int} (De Santis et al., 2010) or by the transverse relaxation rate ($R_2^*=1/T_2^*$). An alternative approach to take into account field inhomogeneity is modeling the T2 decay as fractional order (Reiter et al., 2016).

The Δχ inhomogeneity in the brain parenchyma mainly arises from the presence of diamagnetic myelin sheaths and paramagnetic iron-laden cells, and determines local magnetic field distortions, which affect both the magnitude and phase of the MR signal (Yablonskiy and Haacke, 1994). In the white matter (WM) the iron content does not vary substantially across fiber bundles (Li et al., 2009), nor does myelin density, despite the presence of magnitude and frequency differences in GRE signal observed among myelinated fibers. It is rather the orientation of myelinated fiber bundles with respect to $\mathbf{B_0}$ that affects both phase and amplitude of the GRE signal decay (Yablonskiy and Haacke, 1994; Chen et al., 2013; Rudko et al., 2014). Indeed, recent studies showed that R_2^* in WM tracts perpendicular to $\mathbf{B_0}$ is double than that of in parallel fibers (Sati et al., 2012).

In this work, we aim at highlighting, for the first time in brain tissue, that AD γ-metrics, which are known to depend on water multi-compartmentalization, also depend on magnetic susceptibility, when quantified by DW-MRI. The working hypothesis of the γ-imaging method is that γ-contrast embodies information deriving from both Δχ-maps and DW-maps. Therefore, with the goal of investigating the potential ability of γ MRI technique in reflecting the Δχ anisotropy distribution in human brains, we planned to obtain AD (Mγ, Aγ, axial-γ and radial-γ) and R_2^* parametric maps of the human brain in 8 healthy subjects, and test the correlation between the AD-derived parameters and R_2^*. Mean values of AD-metrics in WM regions including fibers with different orientations with respect to $\mathbf{B_0}$ and in GM regions characterized by different iron contents will be investigated, and compared with values of Δχ taken from literature, and with measured R_2^*.

2. Materials and methods

2.1. Data acquisition

This study was approved by the Scientific Ethics Committee of Santa Lucia Foundation (Rome, Italy). Eight healthy volunteers (4 men, 4 women; mean age ± standard deviation [SD]=25 ± 1 years) participated in this study, after providing informed written consent, according to the national laws and to the local ethics committee guidelines. None of the subjects had a history of stroke or head injury, nor of any other neurological or psychiatric disease. The volunteers underwent MRI examination using a 3.0 T Siemens Magnetom Allegra (Siemens Medical Solutions, Erlangen, Germany), with a circularly polarized transmit-receive coil. The maximum gradient strength was 40 mT/m with a maximum slew rate of 400 T/m/s. The same MRI protocol was applied to all the subjects, including T_2^*-weighted images (T_2^*WIs), and Diffusion Tensor Imaging (DTI) scanning. Particular care was taken to center the subject in the head coil and to restrain the subject's movements with cushions and adhesive medical tape.

T_2^*WIs were acquired using an Echo Planar Imaging sequence (EPI) with TR=5000 ms, flip-angle=90°, 4 different TEs=(10, 20, 35, 55) ms, matrix size=128×128, number of axial slices=32; slice thickness=3 mm, in-plane resolution=1.8×1.8 mm^2; Diffusion-Weighted Double Spin-Echo-Echo Planar Imaging (DW DSE-EPI) was acquired with TR/TE=6400 ms/107 ms; Δ/δ=72 ms/35 ms, and with the same geometry of T_2^*WIs. DW-Images (DWIs) were collected by using Diffusion-sensitizing gradients along 20 non-collinear directions at 14 different b-values (100, 200, 300, 400, 500, 700, 800, 1000, 1500, 2000, 2500, 3000, 4000, 5000) s/mm^2 plus the b=0 (b0) image with no diffusion weighting. The b-values were changed by varying the diffusion gradient strength and keeping Δ and δ constant. The number of sample averages (NSA) was 2 for each b-value, and the total acquisition time for the DW DSE-EPI protocol (applied without the use of parallel imaging) was approximately 52 min. An anterior-posterior phase encoding direction was used for all the scans. The axial slice package was positioned parallel to the anterior-posterior commissure axis and perpendicular to the mid-sagittal plane.

2.2. Data analysis

All the schematic steps describing the image processing are illustrated in Fig. 1.

The pre-processing of data was performed with the use of FMRIB Software Library, v5.0 (FSL, (Jenkinson et al., 2012)). The T_2^*WIs were realigned to the image acquired with TE=10 ms, in order to correct for head movements, via a 6 degrees of freedom (DOF) transformation, using the FSL linear image registration tool (FLIRT) (Jenkinson et al., 2002). The T_2^*WI acquired with TE=10ms was then registered to the b0-image, via a 12 DOF affine transformation with Normalized-Correlation cost function and tri-linear interpolation. Finally, the combination of the two transformation matrices was applied to all T_2^*WIs. The DWIs were realigned with respect to the b0 and corrected for eddy-current induced distortions and subjects' movements, adopting the b0-image as a reference image, with the use of EDDY tool, which had shown better performances compared to the FSL's earlier *eddy_correct* function (Graham et al., 2016). The DTI maps were extracted using all the DWIs acquired up to b=1500 s/mm^2