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On the relationship between cellular and hemodynamic properties of the human brain cortex throughout adult lifespan

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ABSTRACT

Establishing baseline MRI biomarkers for normal brain aging is significant and valuable for separating normal changes in the brain structure and function from different neurological diseases. In this paper for the first time we have simultaneously measured a variety of tissue specific contributions defining $R2^*$ relaxation of the gradient recalled echo (GRE) MRI signal in human brains of healthy adults (ages 22 to 74 years) and related these measurements to tissue structural and functional properties. This was accomplished by separating tissue ($R2^*_t$) and extravascular BOLD contributions to the total tissue specific GRE MRI signal decay ($R2^*$) using an advanced version of previously developed Gradient Echo Plural Contrast Imaging (GEPCI) approach and the acquisition and post-processing methods that allowed the minimization of artifacts related to macroscopic magnetic field inhomogeneities, and physiological fluctuations.

Our data (20 healthy subjects) show that in most cortical regions $R2^*_t$ increases with age while tissue hemodynamic parameters, i.e. relative oxygen extraction fraction (OEF_{rel}), deoxygenated cerebral blood volume (dCBV) and tissue concentration of deoxyhemoglobin (C_{deoxy}) remain practically constant. We also found the important correlations characterizing the relationships between brain structural and hemodynamic properties in different brain regions. Specifically, thicker cortical regions have lower $R2^*_t$ and these regions have lower OEF.

The comparison between GEPCI-derived tissue specific structural and functional metrics and literature information suggests that (a) regions in a brain characterized by higher $R2^*_t$ contain higher concentration of neurons with less developed cellular processes (dendrites, spines, etc.), (b) regions in a brain characterized by lower $R2^*_t$ represent regions with lower concentration of neurons but more developed cellular processes, and (c) the age-related increases in the cortical $R2^*_t$ mostly reflect the age-related increases in the cellular packing density.

The baseline GEPCI-based biomarkers obtain herein could serve to help distinguish age-related changes in brain cellular and hemodynamic properties from changes which occur due to the neurodegenerative diseases.

Introduction

Although it is well known that aging can cause functional cognitive impairments, the neurobiological effects of normal aging (i.e. changes in the cellular content and organizations, including the cerebral cortical thinning and atrophy) on functional and structural declines are still not well understood (Morrison and Hof, 1997). A conventionally accepted idea dating back to 1950s is that the age-related cognitive functional decline is caused by the loss of neurons (Brody, 1955; Coleman and Flood, 1987). However, quantitative studies with newly developed stereological methods suggest that neuron death is not sufficient to account for the age-related functional decline and the number of neurons in the neocortex remains largely the same over adult life (Morrison and Hof, 1997). A more recent point of view is that relatively subtle alterations in the synaptic connectivity, dendritic spine density and neural plasticity (Fjell et al., 2014; Dickstein et al., 2013; Hof and Morrison, 2004; Morrison and Baxter, 2012) can be associated with age-related cognitive dysfunctions. Most of the cited studies related to neuronal structure were performed on non-human primates or other animals, or on post-mortem human tissues. To study neurodegenerative disorders, it is important to separate the normal aging effects from the underlying neurodegenerative pathologies. Hence it is essential to

Abbreviations: GEPCI, Gradient Echo Plural Contrast Imaging; $R2^*_t$, tissue specific $R2^*$; Th, the cortical thickness; $SR2^*_t$, the product of the median $R2^*_t$ and the cortical thickness; OEF, oxygen extraction fraction; dCBV, deoxygenated cerebral blood volume; C_{deoxy}, the concentration of deoxyhemoglobin; VSF, voxel spread function.

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study the age-related cellular and functional alterations quantitatively in vivo and to establish a baseline for distinguishing normal aging from pathological effects.

Magnetic resonance imaging (MRI) is a well-established powerful non-invasive tool to study the brain structure and function in vivo. For example, diffusion MRI can probe the tissue structure on a cellular scale and provide the information on the neural architecture and physiological changes (Le Bihan, 2003), BOLD (Blood-Oxygen-Level-Dependent) MRI (Ogawa et al., 1990) provides information on brain functions (Bandettini et al., 1992; Kwong et al., 1992; Ogawa et al., 1992; Frahm et al., 1993) and high-field phase images allow in vivo visualization of the cortical substructures (Duyn et al., 2007).

In this study, the MRI-based Gradient Echo Plural Contrast Imaging (GEPCI) technique (Luo et al., 2012; Yablonskiy, 2000; Sati et al., 2010) is utilized to establish quantitative in vivo biomarkers characterizing the evolution of tissue structural, cellular and functional properties throughout adult human lifespan. GEPCI is a post-processing method generating a multitude of quantitative and "weighted" images from a single acquisition of GRE signal with multiple gradient echoes. In this paper we mainly use GEPCI quantitative measurements of the transverse relaxation ($R2^*$) of gradient echo MRI signal and GEPCI T1-weighted images. We also use a novel advanced approach (Ulrich and Yablonskiy, 2015) to separate the total $R2^*$ relaxation into tissue-specific ($R2^*_t$) and BOLD-related contributions.

Previously we have published several studies to validate different aspects of the technique that we are using in the current paper. Specifically, we have developed a theoretical model of BOLD effect (Yablonskiy and Haacke, 1994), validated it in phantom studies (Yablonskiy, 1998), conducted detailed measurements of blood magnetic susceptibility (Spees et al., 2001), validated our model in vivo using a rat model (He et al., 2008), and provided analysis of systematic errors due to diffusion effects (Dickson et al., 2011) and errors due to noise in the data (Wang et al., 2013). In Appendix B of this paper, we provide additional analysis of errors specific to the method that is used in this paper.

Since the transverse relaxation of MRI signal is known to be affected by macroscopic field inhomogeneities (Yablonskiy, 1998), in this paper we use a newly-developed approach – voxel spread function method (Yablonskiy et al., 2013a) – that allows minimizing the contribution of these adverse effects, thus providing measurements of *tissue-specific* $R2^*$-related relaxation properties. Further improvement in our measurements is achieved by utilizing another novel method (Wen et al., 2014) allowing the reduction of the artifacts resulting from physiological fluctuations and scanner instabilities. Both these advances improve the accuracy of our measurements.

Since $R2^*_t$ describes the part of the signal decay resulting from water molecule interactions with cellular and extracellular components of biological tissues, we hypothesize that in the normal brain it can serve as a biomarker of the cortical "cellular packing density" – a parameter mostly proportional to the number of neurons and glia cells in the unit tissue volume – and can potentially identify tissue alterations (see further comments in the Discussion section). BOLD effects (Ogawa et al., 1990; Yablonskiy and Haacke, 1994; Yablonskiy, 1998) describe the relaxation due to the mesoscopic magnetic field inhomogeneities caused by the presence of a blood vessel network. Hence, separating BOLD effects from $R2^*$ allows important information on tissue functional hemodynamic properties, such as, oxygen extraction fraction (OEF), deoxygenated cerebral blood volume (dCBV) and tissue concentration of deoxyhemoglobin (C_{deoxy}) (Ulrich and Yablonskiy, 2015).

In this paper, by comparing our results with the literature data we provide a support for the hypothesis that in a healthy adult brain the tissue-specific $R2^*_t$ can serve as a biomarker of the cortical cellular packing density. We also use this hypothesis to explain the relationships between $R2^*_t$ and the functional data, such as OEF and aerobic glycolysis. The baseline GEPCI-based biomarkers obtained herein could also serve to help distinguish age-related changes in brain cellular and hemodynamic properties from changes which occur due to neurodegenerative diseases, e.g. Wen et al. (2015).

Methods

Subjects

This study was approved by the Institutional Review Board of Washington University School of Medicine. Twenty participants aging from 22 to 74, including 7 male (ages: 22, 26, 29, 35, 37, 42, 65) and 13 female (ages: 23, 28, 33, 42, 45, 46, 50, 52, 56, 57, 61, 61, 74), were recruited in this study. None of the participants had any history of neurological diseases. All participants provided informed consent.

Data acquisition

All subjects were scanned in a 3 T Trio MRI scanner (Siemens, Erlangen, Germany). A 3D multi gradient echo sequence was used to obtain the data. Sequence parameters were: resolution $1 \times 1 \times 2$ mm^3 (read, phase, slab), FOV 256 mm × 192 mm, repetition time TR = 50 ms, flip angle 30°, 10 gradient echoes with first gradient echo time $TE_1 = 4$ ms, echo spacing $\Delta TE = 4$ ms. Additional phase stabilization echo (the navigator data) was collected for each line in k-space to correct for image artifacts due to the physiological fluctuations (Wen et al., 2014). The total acquisition time of GEPCI is 11 min and 30 s. Field inhomogeneity effects were removed by using the voxel spread function (VSF) approach (Yablonskiy et al., 2013a). Standard clinical Magnetization-Prepared Rapid Gradient Echo (MPRAGE) (Mugler and Brookeman, 1990) images with TR/TI/TE = 2200/1100/3.37 ms and the resolution $0.9 \times 0.9 \times 1.5$ mm^3 were also collected for segmentation purposes. The total acquisition time of MPRAGE is 6 min. After the data acquisition, the raw k-space data were read into MATLAB (The MathWorks, Inc.) for the post-processing.

Data analysis and image generation

The image processing was finished in MATLAB (The MathWorks, Inc.) using previously developed algorithm (Ulrich and Yablonskiy, 2015). In brief, after correcting the k-space data for physiological artifacts (Wen et al., 2014), we apply FFT in the phase-encoding directions to get images. 3D spatial Hanning filter is then applied to the data in the image domain. To achieve an optimal signal-to-noise ratio, we use the following equation to combine the data of all channels (Luo et al., 2012):

$$S_n(\mathrm{TE}) = \sum_{ch=1}^{M} \lambda_{ch} \cdot \overline{S}_n^{ch}(\mathrm{TE}_1) \cdot S_n^{ch}(\mathrm{TE}); \quad \lambda_{ch} = \frac{1}{M \cdot \varepsilon_{ch}^2} \sum_{ch'=1}^{M} \varepsilon_{ch'}^2 \tag{1}$$

where the sum is taken over all M channels (ch), $\overline{S}$ denotes complex conjugate of S, λ_{ch} are weighting parameters and ε_{ch} are noise amplitudes (r.m.s.). Index n corresponds to the voxel position (n = x,y,z). This algorithm allows for the optimal estimation of quantitative parameters, and also removes the initial phase incoherence among the channels (Luo et al., 2012; Quirk et al., 2009).

The data are then analyzed on a voxel-by-voxel basis using the theoretical model (Yablonskiy, 1998):

$$S(\mathrm{TE}) = A_0 \cdot \exp\left[-R2^*_t \cdot (\mathrm{TE}-\mathrm{TE}_1) + i \cdot 2\pi \cdot \Delta f \cdot (\mathrm{TE}-\mathrm{TE}_1)\right] \cdot F_{BOLD}(\mathrm{TE}) \cdot F(\mathrm{TE}) \tag{2}$$

where TE is the gradient echo time, $R2^*_t = 1 / T2^*_t$ is the tissue transverse relaxation rate constant (describing GRE signal decay in the absence of BOLD effect), Δf is the frequency shift (dependent on tissue structure and also macroscopic magnetic field created mostly by tissue/air interfaces), function $F_{BOLD}(\mathrm{TE})$ describes GRE signal decay due to the presence of blood vessel network with deoxygenated blood (veins