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Quantification of iron in the non-human primate brain with diffusion-weighted magnetic resonance imaging

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ABSTRACT

Pathological iron deposits in the brain, especially within basal ganglia, are linked to severe neurodegenerative disorders like Parkinson's disease. As iron induces local changes in magnetic susceptibility, its presence can be visualized with magnetic resonance imaging (MRI). The usual approach, based on iron induced changes in magnetic relaxation (T2/T2′), is often prone, however, to confounding artifacts and lacks specificity. Here, we propose a new method to quantify and map iron deposits using water diffusion MRI. This method is based on the differential sensitivity of two image acquisition schemes to the local magnetic field gradients induced by iron deposits and their cross-term with gradient pulses used for diffusion encoding. Iron concentration could be imaged and estimated with high accuracy in the brain cortex, the thalamus, the substantia nigra and the globus pallidus of macaques, showing iron distributions in agreement with literature. Additionally, iron maps could clearly show a dramatic increase in iron content upon injection of an UltraSmall Particle Iron Oxide (USPIO) contrast agent, notably in the cortex and the thalamus, reflecting regional differences in blood volume. The method will benefit clinical investigations on the effect of iron deposits in the brain or other organs, as iron deposits are increasingly seen as a biomarker for a wide range of diseases, notably, neurodegenerative diseases in the pre-symptomatic stage. It also has the potential for quantifying variations in blood volume induced by brain activation in fMRI studies using USPIOs.

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Introduction

There is growing evidence that iron naturally accumulates in the brain with aging, mainly within basal ganglia, and that pathological iron deposit plays a role in the pathophysiology of neurodegenerative diseases such as Parkinson's disease (PD) (Griffiths and Crossman, 1993; Griffiths et al., 1999; Berg and Youdim, 2006; Oshiro et al., 2011). Because of their paramagnetic magnetization properties in the field of MRI scanners, iron deposits are responsible for local changes in bulk magnetic susceptibility (BMS) which, in turn, are responsible for small local magnetic field gradients, resulting in a signal loss in the images acquired with gradient-echo sequences due to intravoxel dephasing and an increase in transverse relaxivity (overall increase of R2/R2* relaxivity) (Milton et al., 1991; Antonini et al., 1993; Schenker et al., 1993; Gorell et al., 1995; Brass et al., 2006). Several MRI methods have been developed based on this effect to detect and quantify iron in the brain (Milton et al., 1991; Antonini et al., 1993; Schenker et al., 1993; Gorell et al., 1995; Brass et al., 2006; Haacke et al., 2005; Hardy et al., 2005; Wallis et al., 2008; Péran et al., 2009; Aquino et al., 2009; Deistung et al., 2013; Sedlacik et al., 2014; Jensen et al., 2009) investigate iron presence in normal aging subjects (Aquino et al., 2009; Sedlacik et al., 2014) and in patients with neurodegenerative diseases, such as PD (Wallis et al., 2008; Péran et al., 2009; Graham et al., 2000) or traumatic brain injury (Raz et al., 2011). However, these methods of quantification suffer from the fact that iron induced BMS effects are not the unique source of signal phase shifts and R2 changes in tissues (Deistung et al., 2013; Sedlacik et al., 2014).

On the other hand, the BMS effects induced by iron are responsible for small local magnetic field gradients, which in the context of diffusion MRI, produce significant cross-terms with the programmed gradient pulses inserted for diffusion encoding, resulting in an underestimation of the measured Apparent Diffusion Coefficient (ADC), as evidenced with the decrease of ADC observed after administration of Ultrasmall Particle Iron Oxide (USPIO) in the liver (Zhong et al., 1991; Does et al., 1999). Contrary to the R2/R2* effect which cannot be fully reversed, this effect on the ADC can be eliminated when using diffusion MRI sequences immune to effects of local magnetic field gradients, such as sequences made of "bipolar" gradient pulses (BPG) instead of the usual "monopolar" gradient pulses (MPG) (Zhong et al., 1998; Song et al., 1999; Reese et al., 2003). Hence, in the presence of iron deposits

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a direct comparison of diffusion images acquired with the BPG and MPG sequences could reveal the presence of local field gradients, and, thus, the presence of iron. In this study we have developed this concept to quantify iron deposits. Measurements have been done in the brain of non-human primates of various ages and compared with estimated endogenous iron concentration in the cortex, thalamus and basal ganglia (substantia nigra and globus pallidus). Measurements were also obtained after the injection of USPIOs to increase brain iron content in a controlled manner. Those USPIO results suggest the potential of the approach for perfusion and functional MRI studies.

Theory

Iron particles create local magnetic field gradients which cause a signal reduction in the tissue through static spin dephasing (gradient-echo sequences) and diffusion (gradient-echo and spin-echo sequences). In the presence of such local gradients the measured ADC can be artifactually decreased when using usual (monopolar) diffusion MRI sequences (Zhong et al., 1991; Does et al., 1999; Kennan et al., 1995; Kiselev, 2004). This effect results from the presence of cross-terms between the local background gradients induced and the applied diffusion-encoding pulsed gradients. This ADC decrease may appear counterintuitive, but is well explained by the nonlinear relationship between the diffusion signal attenuation with the b value: the negative cross-term contribution to increase the signal level (decrease in local effective b value) is higher than positive cross-term contribution which decreases the signal level (increase in local effective b values). Assuming the distribution of negative and positive cross-terms is approximately equal, this asymmetry in the effect on the signal level results in an overall decreased effective b value, or, in an artifactually decreased ADC. The effect can be quantified by a correction factor, ξ, to the b value, which depends on the measurement (diffusion) time and the variance of the local gradients (Zhong et al., 1991), and increases with the iron particle intrinsic relaxivity and concentration, [Fe], so that the diffusion signal attenuation, S becomes:

$$S = S_0 . \exp\left\{-b.\left(1\text{-}\xi_{[Fe]}\right).ADC\right\} \equiv S_0 . \exp\{-b.ADC'\} \quad (1)$$

with

$$ADC' = \left(1-\xi_{[Fe]}\right).ADC \quad (2)$$

S_0 is the signal at b = 0. Ignoring iron effects, fitting of diffusion MRI data with Eq. (1) would lead to ADC′ with ADC′ < ADC. When using a *bipolar* (BPG) gradient pulse sequence the effect of cross-terms disappears ($\xi_{[Fe]} = 0$), so that the ADC is correctly estimated. BMS related effects on relaxivity R2/R2* are included in S_0 which contains an implicit exp(-TE.R2) term (TE = echo time).

A limitation of Eq. (1), however, is that diffusion is described by a single ADC which does not adequately reflect water diffusion behavior in tissues. Diffusion in tissues, in particular brain tissues, is not free and therefore molecular displacements do not follow a Gaussian distribution. As a result, signal attenuation plots of ln(S) versus b value are curved and do not follow a straight line, even in the absence of BMS effects, as would be expected from Eq. (1). Several models have been proposed to explain this curvature effect. One empiric way to describe this curvature (and the deviation from Gaussian diffusion) is to develop the signal attenuation as a cumulant expansion (Taylor series) (Chabert et al., 2004; Jensen and Helpern, 2010). Eq. (1) then becomes (limiting to the second order term):

$$S = S_0 . \exp\left[-b.\left(1\text{-}\xi_{[Fe]}\right).D + K.\left(b.\left(1-\xi_{[Fe]}\right).D\right)^2/6\right] \equiv S_0 . \exp\left[-b.D' + K.\left(bD'\right)^2/6\right] \quad (3)$$

with $D' = (1 - \xi_{[Fe]})$. D, where D is now the intrinsic diffusion coefficient when b reaches 0 and K is called kurtosis (related to the 4th moment of the molecular displacement in the narrow gradient pulse regime). D can be directly estimated from Eq. (3) using a BPG sequence ($\xi = 0$), so that the iron related parameter can be obtained (estimating D′ from Eq. (3) with a MPG sequence) as:

$$\xi_{[Fe]} = 1-D'/D. \quad (4)$$

Materials and methods

Non-human primates

Four male rhesus monkeys (*Macaca mulatta*), (7 yo/11.3 kg, 13.5 yo/10.5 kg, 9 yo/7.4 kg, 13 yo/8.6 kg) were housed individually or paired, with a 12:12 h light–dark cycle. The study was conducted in accordance with the European convention for animal care (86-406) and the National Institutes of Health's Guide for the Care and Use of Laboratory Animals. Animal studies were approved by the institutional Ethical Committee (CETEA protocol #10-003).

MRI acquisition

Series of images were acquired on a 3 T MRI scanner (Siemens Tim Trio, Erlangen, Germany) using a 4-channel phased-array transmit-receive coil with a diffusion-weighted echo-planar imaging (EPI) sequence. The number of image acquisitions and the parameter of the sequences were set to maintain the total examination time within acceptable limits to maintain the status of the anesthetized animals stable. The MPG sequence parameters were: TE/TR = 89/3000 ms, FOV = 128 mm, matrix = 64 × 64, 15 slices of 2-mm thickness in the axial direction, and b = 0, 200, 600, 1000, 1400, 1800, 2200, 2600, and 3000 s/mm^2. The same parameters were used for the BPG sequence (twice refocused spin-echo sequence) except for the bipolar gradient pulses (Song et al., 1999; Reese et al., 2003). All BPG pulses had an equal duration (9.4 ms separated by a 9.4-ms interval) to fully cancel cross-terms and the 2 gradient pairs were separated by a 16-ms interval. For the MPG and BPG sequences gradient pulses were applied simultaneously on X, Y and Z axes (gradient vector = [1, 1, 1]), as diffusion anisotropy effects were not relevant to this study. Each acquisition was repeated 6 times for averaging in order to increase signal to noise ratio (SNR). A 3D MPRAGE (TR/TE = 2200/3.2 ms, FOV = 154 mm, matrix = 192 × 192, 104 slices of 0.8 mm thickness in the sagittal direction, resulting in 0.8-mm isotropic resolution) was also used to obtain T1-weighted reference anatomical images.

Phantom experiment

The equivalence of the MPG and BPG sequences in terms of quantitative diffusion quantification (as their gradient pulse design is different) was validated using a phantom at room temperature (20–22 °C). The phantom (2-cm-diameter plastic syringe) was filled with cyclohexane (Sigma-Aldrich Chimie, Lyon, France). Regions of interest (ROIs) for measurements were placed on five slices in the center of the syringe (Fig. 1a).

In vivo experiments

The choice of non-human primates was motivated not only by the possibility to use USPIO contrast agents, but also by the similarity in brain anatomical structure and the presence of iron deposits. Monkeys were positioned in a sphinx position using an MR-compatible stereotactic frame. For anesthesia induction, monkeys received an intramuscular injection of ketamine and xylazine (15 mg/kg + 1.5 mg/kg, respectively). Sedation was maintained with continuous intravenous (i.v.) infusion of

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