Introduction

Next to myelin iron is the other major source of MR contrast in the brain. It dominates $R_2^*$, $R_2$ and QSM cortical profiles, MR-contrast in subcortical areas and contributes to white matter contrast. Aiming at methodological breakthroughs like in-vivo Bodmann mapping or MR-based iron quantification, significant theoretical and experimental efforts were devoted to the understanding of iron-induced MR-contrast. Different to the case of myelin, where the relationship between tissue microstructure and MR parameters is widely accepted, the impact of the cellular and subcellular iron distribution is much less explored. Therefore, usually a single set of linear coefficients is employed to relate tissue iron concentration and quantitative MR parameter maps. A major reason for this simplification is a lack of quantitative knowledge on the cellular and subcellular iron distribution. Beyond this, the interplay between tissue microstructure and MR parameters is widely accepted, the impact of the cellular and subcellular iron distribution is much less explored. Therefore, usually a single set of linear coefficients is employed to relate tissue iron concentration and quantitative MR parameter maps. A major reason for this simplification is a lack of quantitative knowledge on the cellular and subcellular iron distribution.

Methods

Post-mortem MRI

Post-mortem human brain blocks (male, 78 years, post-mortem time before fixation 16h, temporal lobe, female, 71 years, post-mortem time before fixation 26h, midbrain) were obtained from the Neuropathology Department of Leipzig University, Germany. $R_1$ maps (isotropic resolution of 0.23mm) were obtained using the MP2RAGE, $R_2^*$ maps and QSMs (isotropic resolution of 0.21mm and 0.06mm) using multi-echo FLASH sequences. QSMs were reconstructed using the HSFID algorithm (Schwere et al. 2012).

Quantitative $R_2^*$ maps of a single slice were obtained using TSE sequence in plane resolution 0.21x0.21mm$^2$ and multi-echo $T_2^*$ sequences. (c) can be seen on the changes of these parameters upon iron removal. Note invasion of QSM contrast for fiber-rich cortical layer (a).

Tissue de-ironing

One sub-sample (temporal lobe) was subjected to a de-ironing procedure. It was incubated in a solution of 2% sodiumdithionite, desferal and 2% sodiumdithionite solved in PBS at 37°C for a period of 15 days to remove the iron in the tissue.

Results

Grey Matter

Iron concentration increases with cortical depth and determines cortical profiles of $R_2^*$ and $\chi$.

Cellular distribution of iron influences MR line shape

In cortical grey matter iron hotspots are localized in sparsely distributed oligodendrocytes and astroglia. Neurons are iron-poor.

In substantia nigra densely packed iron-rich neurons contain most of the iron and dominate the MR-contrast. (a) Cortical profiles of $R_2^*$, iron concentration and myelin volume fraction obtained with LA ICP MSI. Iron and myelin concentrations increase with cortical depth. Elevated level of iron was observed in a thin (0.5 mm) stripe in subcortical white matter. (b) $R_2^*$ and (c) $\chi$ can be seen on the changes of these parameters upon iron removal. Note invasion of QSM contrast for fiber-rich cortical layer (a).

White Matter

Iron-rich patches around small vessels in white matter

Iron in white matter appears in patches with characteristic size of 100-200 μm. The patches are observed in classical Perls’ and Turnbull’s iron stains as well as in quantitative iron maps obtained with LA ICP MSI. They induce substantial 0.5% intra-voxel de-phasing when resolution lower than 0.2 mm is used and therefore contribute to $R_2^*$ in white matter.

R$2^*$ contrast in SWM is driven by iron in oligodendrocytes and fibers

Conclusions

Iron is inhomogeneously distributed in both grey and white matter. Furthermore, different scales of inhomogeneity determine the MR contrast in the different compartments. In grey matter iron rich fibers, and small (1-3μm) micro-, astro- and oligodendrocytes contained most of the iron and were sparsely distributed. In superficial and deep white matter, however, oligodendrocytes somas with the sizes of 5×1.5μm (distance between cells of 20×5μm) and iron rich fibers contained most of the iron. Iron in cell bodies result in Lorentzian line broadening, while iron-rich fibers induces Gaussian line broadening and dominates in white matter.

In addition, patches of enhanced iron concentration around small vessels with a typical size of 100-200μm contribute 10-20% of $R_2^*$ and QSM a in white matter. A different contrast mechanism in brain nuclei where densely packed 20μm large iron loaded neurons dominated the MR contrast. These results provide an important basis for understanding the iron induced MR-contrast and its microstructural underpinnings. Based on these measured microscopic iron distributions and a Gaussian diffusion model we are now in the process of simulating the MR contrast mechanisms in different tissue types.