High resolution T2* and phase contrast of human AD brain tissue at 9.4T: a structural comparison

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Introduction

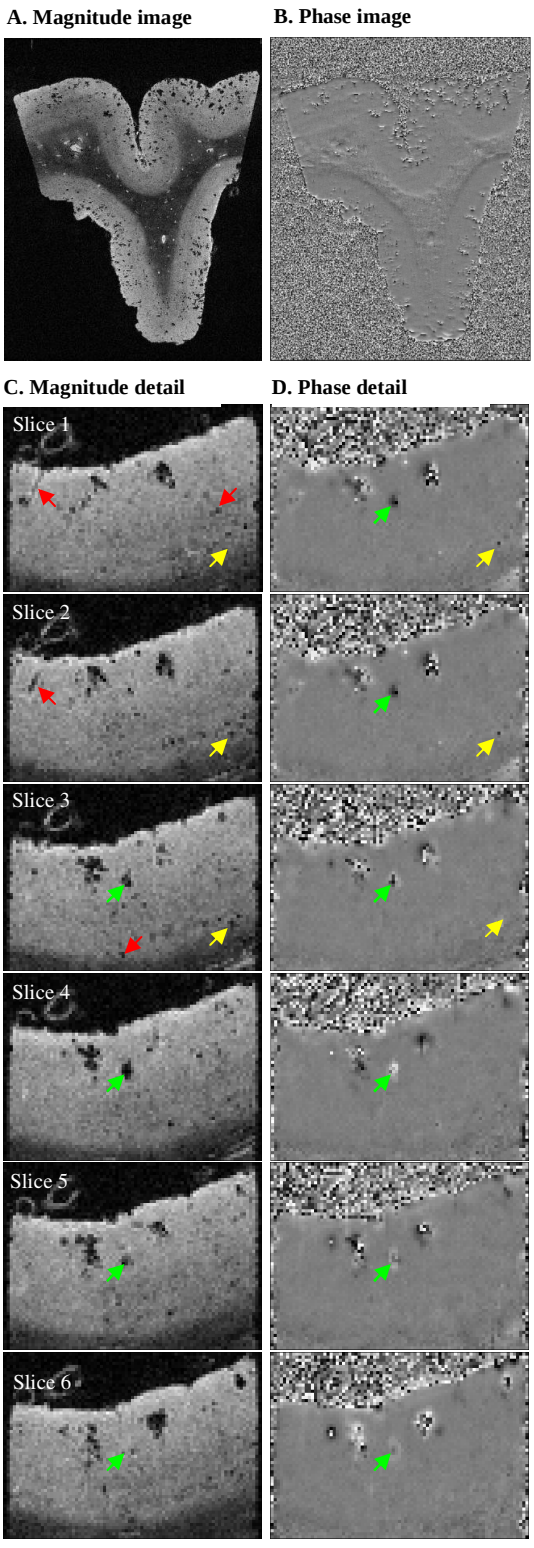
One of the major hallmarks in Alzheimer's disease (AD) is the formation of extracellular amyloid-β depositions or plaques, mainly within the cortex of the brain. Being formed years ahead of clinical symptoms, much interest exists in developing methods for early *in vivo* detections of these Aβ plaques. So far no medical tests have yet been developed to fulfill this goal. Even though MRI has been able to reveal several neuroradiological characteristics, conclusive diagnosis of AD still remains to be made by post mortem microscopic examination. Using AD mouse models, however, successful MRI methods were able to detect plaques both *in* and *ex vivo*. In humans, successful studies have been limited to high field *ex vivo* MRI with some papers claiming to detect amyloid using T2* weighted imaging, while other studies point out many signal voids seemed to be related to cell aggregates with the small vessels instead of correlation to the plaques.[1, 2] The question therefore remains whether Aβ plaques can cause susceptibility effects, allowing their detection using MRI. This is strengthened by the recent availability of new high field whole body MRI scanners creating the potential to exploit these possible susceptibility effects to a further extent with possible *in vivo* applications, e.g. higher resolution. Furthermore, susceptibility effects are directly related to magnetic field strength, as is the phase contrast arising from off-resonance effects. Thus, the combination of magnitude and phase data at high magnetic fields may provide new methods to characterize induced susceptibility effects. [3,4] This study therefore aims to characterize human AD brain tissue using T2*-weighted high field MRI,(9.4T) and comparing the magnitude and phase behaviour of microstructures found in the cortex.

Materials and Methods

Formalin-fixed tissue from the frontal cortex of a pathologically confirmed AD patient was sectioned using a vibratome into a 4x20x20 mm tissue block and rehydrated in PBS 1x for over 24 hours before being placed in customized tissue holder. Filled up with Fomblin (Solvay) air-induced susceptibility artifacts were reduced by extraction under a vacuum. All MRI measurements were conducted using a standard 20 mm volume coil on a vertical wide-bore 9.4T Bruker Avance 400WB spectrometer, with a 1 T $\cdot m^{-1}$ actively shielded imaging gradient insert (Bruker Biospin GmbH, Germany) equipped with ParaVision 4.0 software. A 3D GE T2*-weighted scan (TR/TE = 66/25ms; FA = 10º, NEX = 14) was obtained with 50µm isotropic resolution to create both magnitude and phase images. Phase unwrapping was subsequently performed using a Matlab implementation of the algorithm described in [5].

Results

Figure A shows a single magnitude slice from the 3D GE scan through the *ex vivo* human AD cortex. With an echo time of 25 ms at 9.4T, the image is heavily T2* weighted, and gray to white matter contrast is excellent. The scan resolution is 50 µm isotropic, which should be sufficient to detect microscopic extracellular structures such as amyloid plaques. Immediately apparent are the large number of hypo-intensities in the gray matter. Figure B shows the corresponding unwrapped phase image, which also shows many off-resonance nuclei, mainly in the gray matter. To examine the signal voids and phase shifts in more detail, Figure C and D show a small part of the gray matter for six consecutive slices, for the magnitude and phase images respectively..
Careful examination leads to the following observations, as highlighted by the arrows in Figures C and D. Not all hypo-intense structures visible on the magnitude image create a corresponding effect in the phase image (red arrows), meaning not all hypo-intense structures on T2*-weighted imaging create an observable phase shift. The green arrows show structures that are observable over more subsequent slices in the phase image compared to magnitude image, with the phase change gradually changing sign. In-plane, this corresponds to a gradual phase change from the inside out in a circular fashion. Very small signal voids (yellow arrows) can be observed equally well in the magnitude and phase images. One should note that for very large signal voids, extending over several pixels, the phase images become more difficult to interpret, since the centre of the structure has lost all phase information because of the low signal intensity.



Conclusion / Discussion

Gradient echo brain imaging at high field strengths offers excellent possibilities to visualize small distortions of the magnetic field, offering the potential to detect microscopic structures, such as amyloid plaques. These data clearly show that at high magnetic field, the signal phase provides an additional source of image contrast. The combination of signal voids in the magnitude images and phase contrast may be useful to differentiate between different sources of susceptibility contrast, and thus provide a distinction between amyloid plaques, hemosiderin deposits, microbleeds and other susceptibility sources. Histology of the same tissue block can be used to confirm these findings, and classify the sources of susceptibility contrast.

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