Direct Visualization of β-Amyloid Plaques in Alzheimer's Disease Brain Tissue Using Clinical Field Strength MRI

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Abstract:

   Neuroimaging plays an important supportive role in the clinical diagnosis of Alzheimer's Disease (AD). However there are no human *in vivo* magnetic resonance (MR) imaging techniques that specifically demonstrate the formation of β-amyloid plaques (one of the histopathological hallmarks of AD) and no non-invasive imaging method exists that is able to diagnose AD reliably. High field strength, high resolution MR studies of excised human specimens [1] and *in vivo* AD animal model brain tissue [2] have shown intriguing evidence that MR can detect β-amyloid plaques on the basis of iron co-localization with these plaques [3]. There is now an urgent need for transitional research to develop and validate more clinically-relevant MR techniques that might still permit *in vivo* MR detection of individual β-amyloid plaques in AD patients.

Purpose:

   The aim of this study was to adapt and exploit the highly SNR-efficient and iron-sensitive *Fast Imaging Employing STeady State Acquisition* (FIESTA) MR imaging, now well established from our single-cell MR work [4], for the detection of AD β-amyloid plaques at 3T. 3D FIESTA features an outstanding soft tissue contrast and has been successfully applied to several diagnostic tasks in clinical imaging. Our hypothesis was that individual β-amyloid plaques could be detected in human AD brain specimens, using the common clinical field strength of 3T and an optimized form of the FIESTA pulse sequence. We exploited a specialized gradient insert [5] in order to provide the spatial resolution needed for high-resolution imaging of isolated human brain tissue specimens.
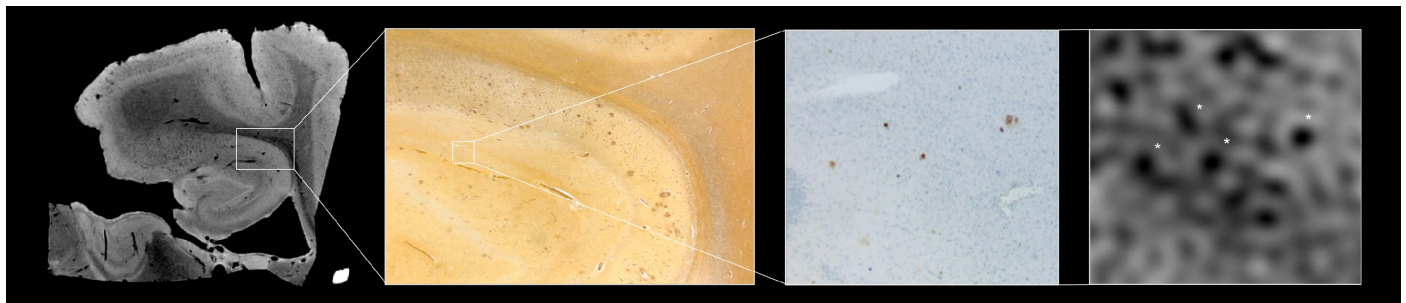

Fig.1) **Human hippocampus and enthorhinal cortex specimen** *featuring multiple focal signal voids with enlarged hippocampal insert of Bielschowsky's stain for plaques and neurofibrillary tangles. Part of the region is further enlarged and shown as a section of the ß-A4 amyloid immunohistochemistry stain and the corresponding FIESTA detail. The pattern of the plaques can be recognized in the MR data.* [*image order from left to right*].

Method:

   MRI was performed on a 3T scanner (GE Signa HD) interfaced with an insertable gradient coil [peak strength: 500 mT/m, max peak slew rate: 3200 T/m/s] and 2cm diameter solenoidal RF coil. Isotropic FIESTA images of autopsy AD brain tissue (Braak&Braak VI; CERAD definite AD) were acquired in 218 minutes [$(100\mu m)^3$; TR/TE 21/11 ms; FA 20°; BW ±8 kHz; phase cycling number/recon: 8/sum-of-squares]. FIESTA datasets were analyzed for the presence of focal signal voids [Fig.2]. Subsequent histological sections were stained for AD plaques and neurofibrillary tangles using Bielschowsky's and for β-amyloid protein using the β-A4-test immunohistochemical staining.
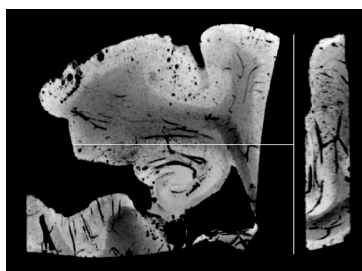
Result:

High-resolution 3DFIESTA imaging revealed spherical signal voids throughout the brain specimen parenchyma. Using a Minimum Intensity Projection (MinIP) technique, tubular intravascular signal voids could be distinguished from spherical intra-parenchymal signal losses [Fig.2]. The latter correlated to plaques in matched histological and IHC sections stained for β-amyloid plaques in the hippocampus and enthorhinal cortex [Fig.1]. We observed correlations between patterns found in MRI and the histological images [Fig.1].

Fig.2) **Minimum Intensity Projection (MinIP)** *of an isotropic tissue slab bearing different signal void structures of tubular and spherical configuration. The right lateral insert demonstrates a coronal cross section.*

Discussion and Conclusion:

   Our group has recently shown the feasibility of direct 3T MRI visualization of amyloid plaques in a novel rabbit model of AD [6]. In contrast to animal models, post-mortem formalin perfusion is not feasible in humans. Consequently human AD brain tissue specimens feature intravascular blood products caused by perimortal stasis. Those blood products give rise to a second paramagnetic intraparenchymal deposition that complicates the task of β-amyloid plaque detection; however, by shape analysis, voids due to β-amyloid plaques can clearly be discriminated from those arising from blood vessels [Fig.2]. Although our gradient insert permits gradient amplitudes and slew rates that are presently not available for human *in vivo* studies with clinical MR systems, this study nonetheless provides important evidence that clinical field strength MR has the intrinsic ability to detect microscopic iron associated with human β-amyloid plaques. Our *ex-vivo* MR imaging technique provides an important translationally-relevant tool for further specific cross-sectional analyses of AD brain.

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