Amyloid Plaque Detection in a Mouse Model at 17.2 Tesla

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INTRODUCTION

Alzheimer's disease (AD) is the most common type of neurodegenerative diseases, and it is mainly characterized by extracellular β-amyloid (Aβ) deposits in the brain in the form of amyloid plaques. These very early lesions in the course of the disease constitute the main target for diagnostics and therapeutics and have previously been identified in mouse models using magnetic resonance (MR) microscopy[1,2]. These plaques typically appear as hypointense spots on T2- or T2*-weighted MR images and their size ranges from 50 µm to 200 µm. One of the challenges in imaging plaques is to achieve high-enough resolution and contrast to detect 50-µm large lesions that are poorly loaded with iron. We have previously demonstrated the detection of Aβ plaques with a gadolinium chelate in the cortex and hippocampus of live animals in a longitudinal study at 7T[3].

As very high-field magnets become available, imaging iron-rich Aβ plaques at a microscopic level becomes possible[4]. We have hypothesized that, together with increased resolution, the increased magnetic susceptibility at very high field would improve the sensitivity of our gradient-echo based protocol for plaque detection. We tested our hypothesis on ex vivo brains at 30 µm isotropic resolution at 17.2 T. For comparison, we have also imaged a brain at 7T with our previous protocol (23x23x90 μm^3) and we registered the 2 brains for plaque-to-plaque comparison.

METHODS

We used 3 APP/PS1De9 mouse brains (12-15 months old), passively stained[5] with a gadolinium chelate (Gd-DOTA) prior to imaging. All MR images were acquired on a 17.2 T magnet (Bruker Biospec 172/25, running Paravision 5.1) with gradients' strength of 1 T/m and a slew rate of 9000 T/m/s. The coil used was a home-built 2-cm surface coil positioned on the mouse brain placed in a home-built holder filled with Fluorinert® (3M) to avoid background signal. The imaging protocol was based on a 3D gradient-echo sequence (FLASH) with TR=32 ms, TE=21 ms, FA=20°, Bw=50 kHz, Matrix=430x384x256, FOV=12.9x11.6x7.8 mm, Nex=8, and Tacq=7h6min. The protocol at 7T was described in [3] (3D FLASH with TR/TE=100/21 ms, Bw=50 Hz/pix, res=23x23x90 μm^3, Nex=8, Tacq=13h50min). Signal and contrast-to-noise ratios (mean SNR over the whole brain and mean CNR between plaque and parenchyma) as well as plaque load (I.e. plaque density averaged over 36 ROIs per brain) were calculated for all brains.

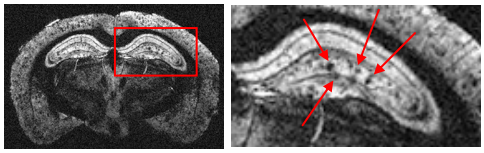

Figure 1: APP/PS1De9 brain imaged at 30 µm isotropic resolution at 17.2 T in 7hrs. Amyloid plaques are shown with arrows on the close-up view of the hippocampus (right).

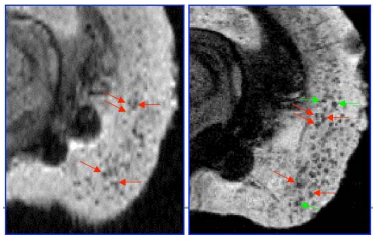

Figure 2: The same amyloid plaques are visible at 7T (red arrows, left) and at 17.2 T (red arrows, right). An increased number of plaques can be detected at 17.2 T (some are indicated with a green arrow, right).

Table 1: Comparison between 7T and 17.2 T data from the same mouse brain.

	SNR	CNR	Plaque load	Plaque size (µm)
7 T	35	26	8.3 %	74.1 ± 3
17.2 T	34	25	9.8 %	96.8 ± 4.1

RESULTS

The results clearly showed amyloid plaques in the cortex and hippocampus of APP/PS1De9 mouse brains (Fig. 1). Very high isotropic resolution (30 µm)^3 was achieved in only 7 hrs. With this very high resolution we were able to detect a larger number of plaques at 17.2 T than at 7 T (Fig. 2): the same plaques could be identified at lower field and at higher field, and additional ones that were not detected at lower field could be detected at higher field (Fig. 2, Table 1). The image quality (SNR and CNR, Table 1) was comparable for the 2 protocols. The calculated plaque load was 8.3 % at 7T vs. 9.8 % at 17 T and the plaque size was larger at higher field than at lower field.

CONCLUSION

This study shows the first images of amyloid plaques at 17.2 T in AD mouse brains at 30 µm isotropic resolution, achieved in only 7 hrs. The improvement in resolution yielded an improvement in the number of plaques detected at 17.2 T vs. at 7 T. The plaques detected at higher field were larger than those detected at lower field due to increased magnetic susceptibility. These results should translate to comparable improvement in sensitivity for in vivo studies of AD mice. The use of very high field magnets should thus highly benefit preclinical imaging of amyloid plaques in mouse models.

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