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Magnetic resonance imaging of amyloid plaques in transgenic mouse models of Alzheimer's disease

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Abstract

A major objective in the treatment of Alzheimer's disease is amyloid plaque reduction. Transgenic mouse models of Alzheimer's disease provide a controlled and consistent environment for studying amyloid plaque deposition in Alzheimer's disease. Magnetic resonance imaging is an attractive tool for longitudinal studies because it offers non-invasive monitoring of amyloid plaques. Recent studies have demonstrated the ability of magnetic resonance imaging to detect individual plaques in living mice. This review discusses the mouse models, MR pulse sequences, and parameters that have been used to image plaques and how they can be optimized for future studies.

Keywords

MR microscopy; Alzheimer's disease; magnetic resonance imaging; magnetic resonance micro imaging; transgenic mice

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by the loss of cognitive function. Because the prevalence of AD increases exponentially after 65 years of age, AD is a leading public health concern as the population ages [1]. The cardinal pathologies of AD are amyloid plaque deposition, cerebral atrophy, and neurofibrillary tangles; however, there are no currently accepted diagnostic tests for AD short of autopsy. It is widely believed that abnormal amyloid metabolism is an early step in the progression to clinical AD; therefore, reducing or preventing amyloid plaque accumulation is a major therapeutic objective in AD research [2].

Transgenic mouse models of AD have been created by inserting one or more of the mutated genes known to cause familial AD in humans [3,4]. The mutations are associated with presenilin 1 (PS1), presenilin 2 (PS2), and amyloid precursor protein (APP). These mouse models allow controlled study of plaque deposition and testing of interventions. Currently the only well-established method of detecting individual amyloid plaques is through post-

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mortem histological analysis. A non-invasive tool to detect and quantify individual plaques in mice would be an invaluable tool, particularly in longitudinal studies where the number of mice in the study can be a limiting factor. Positron emission tomography (PET) ligands such as Pittsburgh Compund B detect fibrillar amyloid β (Aβ) in plaques, but the resolution of PET is too low to identify individual plaques or to quantify plaque density [5-8].

Magnetic Resonance Imaging (MRI) provides the spatial resolution necessary to visualize and quantify plaques with the potential to track individual plaques over time. Amyloid plaques are very small (< 100 μm) compared to typical MRI resolution, so they are difficult to image. Reliable imaging requires very long scan times, so even small improvements in imaging efficiency can significantly increase the feasibility of studies involving large numbers of mice, multiple imaging time points, or both. Despite several reports of successful plaque imaging, the variety of transgenic mouse models and imaging techniques have made it difficult to compare the studies to determine an optimal imaging strategy. Furthermore, imaging plaques in humans is currently far from feasible, but it may be possible after refining imaging techniques on transgenic mice.

Ex Vivo Imaging

The high resolution needed to image amyloid plaques requires long scan times that make some techniques impractical *in vivo*. In 2004 Zhang *et al.* reported *ex vivo* imaging of amyloid plaques in the APP/PS1 mouse model with a spin-echo pulse sequence [9]. They were able to see individual cortical and hippocampal plaques in the fixed *ex vivo* brain of 15.5 month old mice. However, the long scan times (8-24 hr) made *in vivo* imaging with that technique impossible. Also in 2004, Lee *et al.* reported visualizing plaques in the *ex vivo* brain of APP/PS1 mice [10]. This work used a fast-spin-echo (FSE) technique to image cortical and hippocampal plaques, but the imaging time of 10-11 hr was also too long to be translated to *in vivo* imaging.

Faber *et al.* reported bright contrast detection of plaques using the CRAZED sequence [11]. They were able to generate bright contrast from the thalamic plaques of an APP × ADAM10-dn mouse in less than 3 min. However, they determined that the low signal intensity in the image would make CRAZED imaging impractical for routine *in vivo* plaque imaging.

Our group reported the advantage of using susceptibility-weighted imaging (SWI) [12] for *ex vivo* plaque imaging [13]. The SWI method provided high plaque contrast in a relatively short scan time (1hr 30 min). Fig. (1) shows spin-echo and SWI images of *ex vivo* brain of a 9-month old APP/PS1 mouse brain and an *ex vivo* brain of a wild-type (WT) mouse. The plaque contrast in the SWI image is clearly greater, but the SWI method was found to be impractical *in vivo* due the susceptibility artifacts from the air-to-skull interface and the surface vessels.

In Vivo Imaging

In vivo imaging of plaques has proven more difficult than *ex vivo* imaging due to restricted scan times and motion artifacts from the mouse's cardiorespiratory pattern. *In vivo* imaging of amyloid plaques was first reported in 2004 by Jack *et al* [14]. In this work, individual cortical plaques in APP/PS1 mice were visible with an adiabatic spin-echo sequence in a nominal 1 hr 40 min scan. Fig. (2) shows a spin-echo image from a 13 month old APP/PS1 mouse and a wild-type mouse. One can see the lack of hypointensities in the wild-type mouse. The scan was triggered off of the cardiorespiratory pattern, so the actual scan time was slightly longer and varied from mouse to mouse. This work was also the first to compare multiple techniques and parameter sets to optimize the imaging. First, it was

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subjectively determined that a spin-echo sequence was superior to a gradient-echo sequence, then it was subjectively determined that the optimal through-plane resolution was 120 μm given and in-plane resolution of 60 μm × 60 μm. Using this technique it was possible to register *in vivo* MR images, *ex vivo* MR images and histology images to match plaques across the three modalities. Plaques were matched between MRI and histology to determine that the smallest plaque that could be resolved *in vivo* had a diameter of 35 μm [15,16]. It was also demonstrated that the earliest age at which plaques were visible in the APP/PS1 mouse using the adiabatic spin-echo sequence was 9 months. In 2006, Braakman *et al.* imaged the cortical plaques of APP mice using a FSE sequence [17]. The multi-slice FSE sequence allowed them to visualized plaques in a relatively short scan time (25 minutes). This study is currently the only one to report longitudinal imaging of the same mice. Individual plaques were matched between images of the same mouse at 12, 14, 16, and 18 months of age. Borthakur *et al.* were also able to visualize the cortical and hippocampal plaques of APP/PS1 mice *in vivo* using $T_{1\rho}$-weighting [18]. The $T_{1\rho}$-weighting generates sufficient plaque contrast, but the scan time was very long (3 hours) compared to the other techniques, and only a single slice was acquired.

Thalamic plaques have also been imaged by several groups. Vanhoutte *et al.* demonstrated *in vivo* thalamic plaque imaging in APP mice using a gradient-echo pulse sequence [19]. The thalamic plaques of APP/PS1 were also imaged using a gradient-echo sequence by Dhenain *et al* [20]. Faber *et al.* imaged the thalamic plaques of APPxADAM10-dn mice *in vivo* using a fast, low-resolution gradient-echo sequence [11]. Thalamic plaques in all of these mouse models are relatively large and have a high iron concentration; therefore, they can be successfully imaged with a lower resolution than that needed to image cortical plaques [21,22]. These techniques would be unable to see cortical or hippocampal plaques.

Optimizing Plaque Imaging

Our group has chosen the cortical plaques of the APP/PS1 transgenic mouse model as the preferred target for imaging and therapeutic studies. The APP/PS1 mouse model is a well established model with plaque formation beginning at three months of age [22]. Compared to the APP mouse model, the plaques in the APP/PS1 model are generally smaller, more numerous, and also develop more rapidly beginning at a younger age (Fig. (3)). This makes them more difficult to image, but more attractive for therapeutic and longitudinal studies, due to the shorter time and costs required for housing the mice. The cortical, as well as hippocampal, plaques are preferred to the thalamic plaques in the APP and APP/PS1 transgenic mice for MR imaging because they more closely mimic the morphology and distribution of human amyloid plaques. Thalamic plaques are very large and contain high concentrations of iron. This makes them easy to image, but they are not closely related to human amyloid plaques. While both cortical and thalamic plaques are thioflavine S/Congo red positive and are immunopositive for Aβ peptides, cortical and hippocampal plaques in both humans and transgenic mice contain much lower levels of iron that are only detectable by DAB-enhanced Perl's staining [23]. Thalamic plaques are highly visible by standard Perl's (Prussian blue) staining [24]. With regard to anatomical distribution, just like the cortical and hippocampal plaques in APP/PS1 mice, amyloid plaques in humans are also found predominantly in the gray matter of the cerebral cortex and hippocampus. The morphology of thalamic plaques is also different from cortical plaques in humans and transgenic mice. Thalamic plaques have a compact and highly spherical morphology with well-defined, regular margins (unpublished observations). Cortical plaques in both transgenic mice and humans generally have a more irregular shape, displaying a dense core of intense thioflavine S/Congo red staining with irregular fibrils radiating outward. These are generally referred to as neuritic, dense-core, or senile plaques. Diffuse plaques are less common in transgenic mice than humans, but in our experience only thioflavine S-positive

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plaques are detectable by MRI. It is our opinion that if successful MR techniques for imaging individual amyloid plaques in human AD patients are to be developed using AD transgenic mouse models, then only the pathological features that most closely replicate the human disease should be targeted.

Ex vivo imaging can be used as a tool to empirically compare and optimize *in vivo* imaging techniques, since performing more than two or three scans in a single session is impossible *in vivo*. Recently two reports have focused on using *ex vivo* imaging to analyze and optimize amyloid plaque imaging [13,25].

Meadowcroft *et al.* used a novel histological coil to image 60 μm thick slices of brain tissue [25]. The slices were then stained for histologic analysis. This technique allows perfect registration between the 2D MRI and the histologic images. This method was performed on both human AD tissue and APP/PS1 tissue. The MR images were compared to thio-S stains and iron stains to determine the properties of plaques that were MR visible. It was concluded that the contrast generated by plaques in APP/PS1 mice was most likely via decreased T_2 due to dense fibrillar Aβ deposits, not via decreased T_2* due to high iron concentration. Our group corroborated this theory by mapping T_2, T_2*, T_1 and proton density in *ex vivo* samples [13]. We found that T_1 and proton density did not contribute to plaque contrast, and that the T_2 and T_2* values were very similar in plaques (32.1 ms and 31.1 ms, respectively). This indicates that the dominant mechanism of plaque contrast is due to increased transverse relaxation rate, probably due to dense Aβ aggregates. If the iron concentration were high inside the plaque, one would expect that T_2* would be significantly different than T_2.

Although there have been many reports of successful plaque imaging, no two groups have used the same pulse sequence or parameters. Our group used *ex vivo* imaging to compare the plaque contrast generated by a variety of pulse sequences in order to determine which sequences provide greater plaque visibility [13]. We found that fast-spin-echo techniques are inferior to techniques that average multiple echoes for a given total scan time. This is because the T_2 decay between echoes causes blurring in the final image [26]. Since plaques are typically smaller than a single voxel, any blurring will significantly degrade the plaque visibility. We also determined that the greatest plaque contrast can be generated *ex vivo* by a multi-gradient-echo based SWI sequence. Unfortunately, we found that this sequence would be impractical *in vivo* due to the very long echo time required to get optimal T_2* and phase contrast. Therefore, we concluded that the optimal *in vivo* pulse sequence was a multi-asymmetric-spin-echo sequence with less than 8 ms of spin-echo asymmetry.

Summary

MR imaging of amyloid plaques in mouse models of AD has proven possible and reliable, but there are still no reports of it being used as a tool in a therapeutic study. Recent studies have gone beyond proof of principle to optimization and analysis of plaque contrast [13,25], but there is still room for improvement. Previous studies have based the image resolution on qualitative image sharpness and plaque contrast. A quantitative analysis of the imaging efficiency for a range of image resolutions could significantly improve plaque imaging efficiency. Also, a more detailed analysis like that done by Meadowcroft could illuminate the differences between plaques that are MR visible and those that are MR invisible in order to better design experiments. Even without these further improvements, we believe that plaque imaging can be valuable tool for AD research in mice.

With enough optimization and understanding of plaque imaging in mouse models, it is possible that human plaque imaging will be realized. The difficulties in moving from mouse imaging to human imaging are many. First, the movement artifacts will be much larger since

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a human patient will not be immobilized and anesthetized as a mouse is. Second, the imaging time will need to be reduced to a more reasonable length – less than 10 minutes would be ideal. Third, the human brain is much larger than the mouse brain, so the FOV used for typical human clinical MRI will need to be severely reduced to a restricted area of interest within the human brain. The most attractive targets for reduced FOV imaging would be the lateral temporal, prefrontal, or parietal cortex because these areas have high plaque loads but are also close to the surface, so a surface coil could be used to achieve maximal SNR. Despite the difficulties, there are a couple ways in which human plaque imaging may be easier. First, the location of interest in humans will be further from the sources of susceptibility interfaces than in mice; therefore, SWI may be feasible. This is advantageous because we found that SWI can provide significantly greater plaque contrast than other techniques. Second, human plaques contain more iron than APP/PS1 cortical plaques [25], so the SWI contrast will be significantly higher. Because these advantages of human plaques, it is our opinion that the most significant hurdle in human plaque imaging is patient motion. If motion can be adequately accounted for, human plaque imaging should be possible.

Acknowledgments

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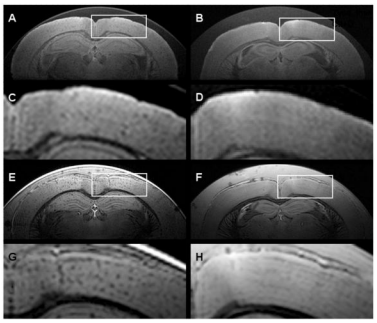

Fig. (1).
Comparison of spin-echo and SWI images of *ex vivo* APP/PS1 and WT mouse brains. (**A**) and (**C**) Spin-echo image of an APP/PS1 brain, with (**C**) representing the magnified box in (**A**). (**B**) and (**D**) Spin-echo image of a WT brain. (**E**) and (**G**) SWI image of an APP/PS1 brain. (**F**) and (**H**) SWI image of a WT brain.

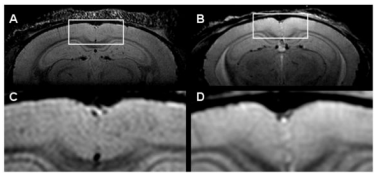

Fig. (2).
In vivo images using a multi-asymmetric spin-echo sequence. (**A**) and (**C**) Images of a 13 month old APP/PS1 mouse. (**B**) and (**D**) Images of a 4 month old WT mouse.

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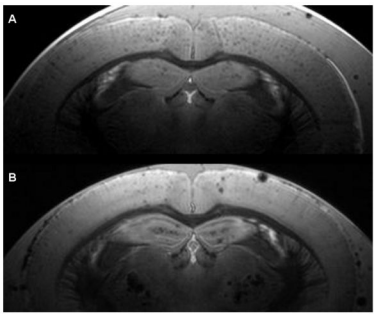

Fig. (3).
Comparison of a 9 month old APP/PS1 brain (**A**) and a 22 month old APP brain (**B**). Even at less than half the age of the APP mouse, the APP/PS1 mouse has more numerous but smaller plaques.