Amyloid plaques detection by MRI: comparison of five mouse models of amyloidosis

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Target Audience: Scientists interested in detection of amyloid plaques by MRI in mouse models of Alzheimer's disease.

Purpose: Alzheimer's disease (AD) is characterized by two complementary microscopic brain lesions: amyloid plaques and neurofibrillary tangles. Amyloid plaques occur up to 20 years before the first clinical signs of the disease [1]. Imaging these plaques is thus critical for an early diagnostic of AD and to follow-up potential treatments. Several efforts aim at developing methods for amyloid plaque detection with high-resolution magnetic resonance imaging (MRI). Recently our group developed methods of *ex vivo* [2] or *in vivo* [3] amyloid plaques detection based on the use of a non-targeted Gadolinium (Gd) contrast agent. Numerous mouse models of amyloidosis have been developed to study the mechanisms of AD (http://www.alzforum.org/res/com/tra/default.asp). These mice are mainly obtained by genetic modification of the Amyloid Precursor Protein (APP) and/or the presenilins (PS) proteins. Even if all these mouse strains develop amyloid plaques, the age of appearance, the size and the composition of the plaques are different [5-6]. Here, we compared the MRI detection of amyloid plaques by *in vivo* and *ex vivo* Gd-staining in five different strains of mouse model of amyloidosis. We show that amyloid plaques are detected with quite different efficiency depending on the strain. Thus, considering the strain is an essential step prior to MRI studies that aim to detect amyloid.

Methods: Five strains of mouse model of amyloidosis were used: $APP_{sl}/PS1_{M146L}$, APP/PS1dE9, B6.PS2APP, APP-SDI and 3xTg ($APP_{swe}/PS1_{M146VKI}/Tau_{P301L}$) aged of 14-15 months (n=2/strain) were used. All these strains develop amyloid plaques before 10 months [5-6]. Experiments were performed as previously described [4]. Prior to *in vivo* MRI experiments, mice anesthetized with isoflurane (1%) received an intracerebroventricular (ICV) injection of Gd (DOTAREM®, 500mM, 1μl/side). After 1 hour of diffusion, *in vivo* MR images were acquired (3D-GE: 29*29*117μm^3, TR/TE=50/13ms, α=20°, Nex=2, Acq time=1h49min). Mice were then perfused (PFA 4%) and their brains were extracted and post-fixed overnight before incubation in a Gd solution (DOTAREM® diluted at 2.5mM in PBS) for 48 hours. Brains were placed in a tight plastic tube filled with an aprotonic perfluorocarbon-based fluid (Fluorinert®) that provides a black background for the *ex vivo* high-resolution 3D-GE sequence (25*25*100μm^3, TR/TE=40/15ms, α=20°, Nex=16, Acq time=11h39min).

Results: Following *in vivo* ICV infusion of Gd, MR images show high signal enhancement compared to non-injected mice in which no plaques can be detected (see [3-4] for examples). Numerous hypointense spots were revealed by the Gd-staining procedure (Fig.1, upper pictures) which was previously demonstrated to detect amyloid plaques [3-4]. The number, size and contrast of the hypointense spots were highly variable in the different strains. This inter-strain difference was confirmed by the high signal/noise ratio *ex vivo* Gd-stained MR images (Fig.1, lower pictures). Plaques were more visible in $APP_{sl}/PS1_{M146L}$ > B6.PS2APP > APP/PS1dE9 > APP-SDI > 3xTg mice and only few plaques appeared in the two latter strains. The $APP_{sl}/PS1_{M146L}$ strain presented large plaques as compared to B6.PS2APP or APP/PS1dE9 which is consistent with previous histological reports at 2.5 months in the $APP_{sl}/PS1_{M146L}$ mice [7]. Strikingly, only few plaques appeared in the 3xTg mice.
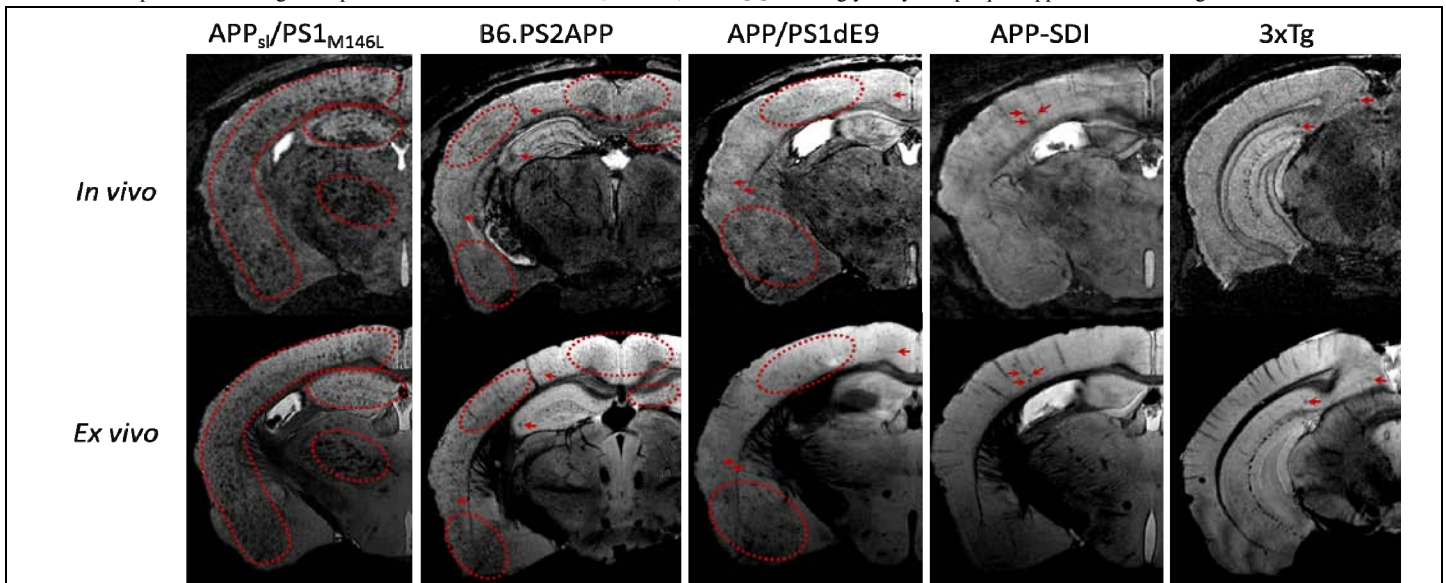

Figure 1: *In vivo* and *ex vivo* detection of amyloid plaques in five different strains of mouse models of amyloidosis. Upper pictures were obtained after ICV *in vivo* infusion of a Gd solution (500mM). Lower pictures were realized in the same mice after a 48 hours incubation of the brains in a Gd/PBS solution (2.5mM). Red arrows show amyloid plaques detected in few areas, whereas red dots outline larger areas where plaques could be detected.

Discussion/Conclusion: These results demonstrate that depending on the strain, amyloid plaques display highly different aspects in MRI. These differences appear to be mainly due to the size of amyloid plaques. The contrast/noise ratio of the plaques on MR images is also critical for the detection of the plaques. This parameter can be modulated by the composition of the plaques, for example by their iron concentration or the Aβ40/42 ratio that can modulate their hydrophobicity and interaction with the contrast agent.

Reference: [1] Sperling et al., *Alzheimer's Dement.* 2011 ; [2] Dhenain et al., *Magn Reson Med.* 2006 ; [3] Petiet et al., *Neurobiol Aging.* 2012 ; [4] Santin et al. *NeuroImage.* 2013 ; [5] Lee and Han, *Exp Neurobiol.* 2013 ; [6] Higgins et al., *Behav Pharmacol.* 2003 ; [7] Blanchard et al., *Exp neurol.* 2003.