Ex vivo detection of cerebral amyloidosis on a human 7 Tesla MRI system.

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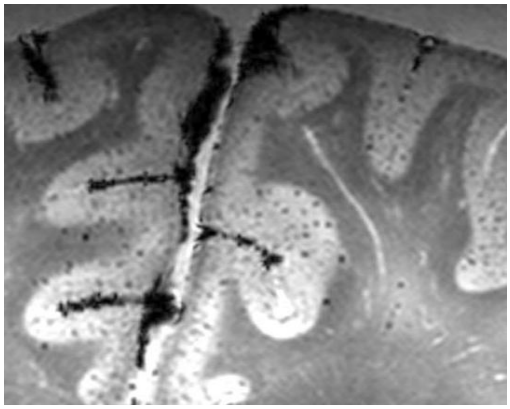
Introduction: Deposition of amyloid-β (Aβ) in the brain is a common pathologic feature of disorders such as Alzheimer's disease (AD), sporadic cerebral amyloid angiopathy (CAA), and some hereditary forms of CAA. Although the feasibility to visualize amyloid plaques in transgenic AD mice with MRI (7T) was established previously (1, 2), the results in human brain tissue are inconclusive (3-5). In the present study we explore the ability of human 7T MRI to detect differences in MRI features of the cerebral cortex in brain specimens of subjects with proven brain Aβ deposition and control subjects lacking such deposition.

Methods: We performed T2- and T2*-weighted MRI with the following parameters: 1. High resolution 0.3 x 0.3 x 0.3 mm (isotropic) 3D T2*-weighted gradient echo images with different echo times and a different number of sample acquisitions with a scan duration of 95 minutes per scan (NSA=8), 47 minutes per scan (NSA=4), 24 minutes per scan (NSA=2) or 12 minutes per scan (NSA=1); repetition time (TR)/echo time (TE) 60/ 20, 25, 30, 35 and 40 ms, flip angle 10°, slice thickness 0.3 mm, 37 slices, no interslice gap, 180 x 99 mm field of view, 600/333 matrix size - resulting in a nominal resolution of 0.3 x 0.3 x 0.3 mm. 2. High resolution 0.3 x 0.3 x 1.0 mm (non-isotropic) 3D T2*-weighted gradient echo images with a different number of sample acquisitions with a scan duration of 14 minutes per scan (NSA=4) or 7 minutes per scan (NSA=2); repetition time (TR)/echo time (TE) 60/ 20 ms, flip angle 10°, slice thickness 1.0 mm, 11 slices, no interslice gap, 180 x 99 mm field of view, 600/333 matrix size - resulting in a nominal resolution of 0.3 x 0.3 x 1.0 mm. 3. High resolution Multi Slice T2*-weighted gradient echo images with different echo times with a scan duration of 9 minutes per scan; TR/TE 750/ 17, 30, 50 ms, flip angle 45°, slice thickness 1.0 mm with a 0.1 mm interslice gap, 15 slices, 240 x 180 mm field of view, 1000/750 matrix size - resulting in a nominal resolution of 0.24 x 0.24 x 1.0 mm, NSA 1 (adapted from Duyn and coworkers (6)). 4. High resolution 3D T2*-weighted gradient echo images with different flip angles with a scan duration of 7 minutes per scan (this type of MRI is usually performed in living subjects); TR/TE 32/ 19 ms, flip angle 10°/15°, slice thickness 1.4 mm with a -0.7 mm interslice gap, 120 slices, 220 x 180 field of view, 880/720 matrix size - resulting in a nominal resolution of 0.25 x 0.25 x 1.4 mm, NSA 1. 5. High resolution 0.3 x 0.3 x 0.3 mm (isotropic) 3D T2-weighted spin echo images with different echo times with a scan duration of 75 minutes per scan; TR/TE 400/ 25, 35 ms, flip angle 90°, slice thickness 0.3 mm, 37 slices, no interslice gap, 180 x 99 mm field of view, 600/333 matrix size - resulting in a nominal resolution of 0.3 x 0.3 x 0.3 mm, NSA 1.The complete scan protocol had a total duration of 18.4 hours. We performed this scan protocol on formalin-fixed samples of cerebral cortex from 6 subjects with AD changes, 7 with CAA and 5 subjects without immunohistochemical evidence of cerebral Aβ deposition. All MRI scans were scored for 2 cortical grey matter features: small granular hypointensities and inhomogeneity (patchiness).

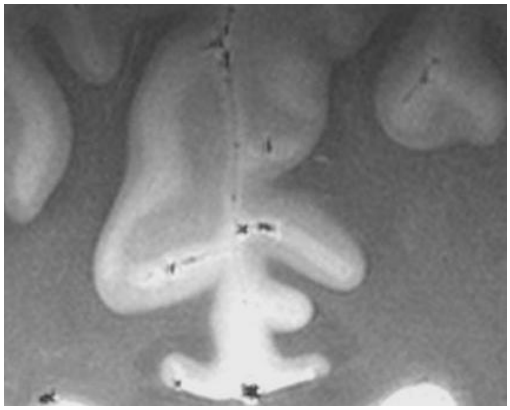
Results: High resolution, 0.3 x 0.3 x 0.3 mm 3D T2*-weighted images revealed granular hypointensities in and/or inhomogeneity of the cortex in all cases with brain Aβ deposition of both AD patients and CAA patients. In none of the control subjects these MRI features were observed. These features were best visualized with echo times between 20 and 30 ms and sample averages between 2 and 8. The features were also visible on the other T2*-weighted images, although it was more difficult to differentiate between brain specimen with Aβ deposition and controls. With the high resolution T2-weighted images the features disappeared in some cases or became very vague.

Conclusion: This study shows that abnormal features can be visualized *ex vivo* with human MRI (7T) in human brain specimens with cerebral Aβ deposition. These features include a: granular hypointense spots, which have the same appearance as the hypointensities representing amyloid plaques observed in earlier studies in AD transgenic mice and human AD (1-3, 5), suggesting that the hypointensities in our images may also represent amyloid plaques. And b: less circumscript changes giving the cortex an inhomogeneous appearance. These changes can be visualized on T2*-weighted sequences, even with clinically acceptable acquisition times, suggesting that these techniques could be useful in a clinical setting.



Granular hypointense spots

Inhomogeneous cortex



Homogeneous cortex

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