Detecting Amyloid-β Plaques in Alzheimer’s disease

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The fundamental pillar of the Alzheimer’s disease amyloid hypothesis that the deposition of Aβ precedes and induces the neuronal abnormalities that underlie dementia has recently conceptually challenged by the hypothesis that alterations in axonal trafficking and morphological abnormalities precede and lead to senile plaques. A general consensus has been reached recently, insofar as disordered metabolism of Aβ protein is central to the pathological cascade that ultimately leads to clinical AD. Consequently, Aβ reduction in humans remains the major therapeutic objective and transgenic mouse models of AD allow controlled study of this process. MRI theoretically provides the spatial resolution needed to resolve single neuritic Aβ deposits. Although currently limited to be applied in human due to unfavorable long acquisition times, MRI has been used to visualize Aβ plaques in AD mouse models. Both AD patients and AD mouse models possess compact and diffuse plaques. The mouse compact plaques display a fibrillar internal structure radiating outward from a central core that is not visible in human compact plaques.

Histological data from postmortem human AD tissue have confirmed focal iron load and iron-binding proteins in Aβ plaques. Ferric iron (Fe²⁺) in brain tissue acts as a natural contrast agent causing faster proton T₂ and T₂* relaxation. It is important to note here that the cause of plaque contrast in mouse model tissue may partly differ from the contrast mechanism suggested for human plaques. The iron content revealed by Perl’s Prussian Blue staining seems to be much lower in AD mouse brain tissue than in the human AD tissue samples, suggesting a different cause of the hypo-intense appearance on T₂ and T₂*-weighted MR images of AD mouse brain regions devoid of ferric iron [1]. In addition AD mice may exhibit regional differences in iron content [2]. The ability to delineate Aβ plaques with MRI using T₂, T₂* as well as susceptibility-weighted-imaging (SWI) has been demonstrated ex vivo (some authors refer to this as in-vitro) with human AD brain samples or samples obtained from AD mouse models (reviewed in [3,4]).

Visualization of plaques using MRI in the living AD mouse puts additional challenges on the MR acquisition due to brain motion originating i.e. from respiration and blood pressure waves. Jack and colleagues [5] in their pioneering work were able to visualize plaques with diameters as small as 50µm based on a native contrast as hypo-intense structures on T₂ or T₂*-weighted images in aged AD mice at a scanning time of less than 2 hours, i.e. approaching a time frame acceptable for in vivo imaging. Further strategies to improve the specificity in Aβ plaque imaging are based on labeling strategies (and delivery approaches) based on positive T₁ contrast agents [6]. In addition recent studies have explored specific detection of parenchymal versus vascular amyloid deposits as well as considering the contribution from cerebral microbleeds, present at late stage of the pathology [7,8].

In my talk, I will review the different approaches and discuss current challenges and limitations in detecting Aβ plaques in-vivo focusing on the following key aspects:

- How to achieve the needed resolution with a sufficiently high signal-to-noise ratio (SNR).
- How to achieve optimal contrast of Aβ plaques
- How to improve specificity and thereby avoid false positives.