Differentiating Microbleeds from Plaque in Alzheimers Disease

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Introduction: Numerous neurological disorders are characterized by the presence of brain lesions which can be detected using MRI. Alzheimer's brain lesions can be broadly categorized into two types: amyloid plaques and microbleeds (Cordonier et al., 2011). Microbleeds result in increased magnetic susceptibility due to blood iron products surrounding blood vessels. However, the relations between iron content and amyloid plaques magnetic susceptibility is less determined.

To assess the performance of newly developed MR imaging methodologies, determination of disease progression and monitor intervention, accurate selection of brain lesions is crucial. In this study, we demonstrate a method for automated detection of amyloid plaques and microbleeds visualised using MRI phase image and susceptibility weighted imaging (SWI) acquired using an ultra-high field magnet. We hypothesised that the phase shifts between amyloid plaques and microbleeds are significantly distinct, and therefore fine-tuning the weighting of the phase map for creating SWI could help distinguishing microbleeds from plaques.

Method: MRI scans were performed on paraformaldehyde fixed brain specimens of 27-month APP23 transgenic mice (n=3, 1 control) obtained from the lab of Prof. Bernd Pichler (Eberhard-Karls-Universität Tübingen, Germany). APP23 mice produce large quantities of cerebral amyloid plaques (Sturchler-Pierrat, 1997). Brain samples were washed in phosphate buffered saline and placed in fomblin (Solvay Solexis, Milan, Italy), or in some cases, saline solution, prior to MRI at 16.4T (Bruker Biospin, Ettlingen, Germany). Acquisition parameters: (1) To establish optimal T_2* weighting, 2D multi gradient echo images (FLASH) were acquired at TR=1500 ms, FA=30° and TE 3.5 to 53.5 ms with 5 ms intervals, with the resolution of 59x59x500µm. (2) Optimum TE to achieve maximum SNR/CNR was 20 ms, so subsequent imaging used this TE with a spatial resolution of 59x59x100 µm (30 mins).

The SW and phase images were calculated using the SWI processing module in ParaVision 5.1 (Bruker Biospin, Ettlingen, Germany). Phase filtering was performed as described by Haacke et al, 2004, with the Gauss broadening set between 0.25 and 1 mm as necessary. The number of multiplications of the phase mask performed ranged from two to eight. Both positive and negative phase masks were used.

The methods for semi-automated lesion selection were written in Matlab (The MathWorks, Natick, MA), based on (1) lesion roi examples from users input, (2) intensity and lesion size thresholding, and (3) positive and negative lesion filtering.

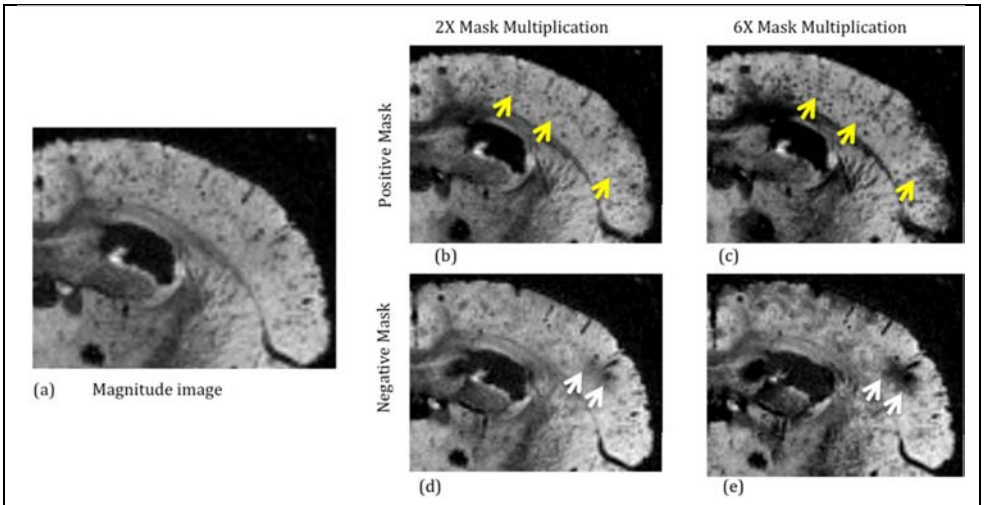

Figure 1. Tissue specific susceptibility contrast can be enhanced by choosing appropriate polarity phase-shift during SWI phase mask multiplications. (a) magnitude image; (b,c) positively and (d,e) negatively weighted SW images, multiplied 2 and 6 times. Plaques (small dark spots, yellow arrows) are accentuated in the positive masked images (b, c), while blood vessels and potential microbleeds (large or rectangular spots, white arrows) are more prominent in the negative masked images (d, e).

Results: Figure 1 shows that most of the cortical lesions in APP23 brains contain amyloid plagues with positive phase shift. The large lesions surrounding blood vessels in the cortex and thalamic areas have negative phase shifts and most likely result from blood iron products from the microbleeds.

Conclusion: Alzeimer's amyloid plaques and microbleeds in APP23 mouse have been demonstrated at 16.4T. Amyloid plaques and microbleeds produced distinct phase shifts: positive for plaques and negative for microbleeds. Histology was performed to verify the accuracy of the two contrast sources.

References: **1**. Haacke, E.M. et al., 2004, Susceptibility weighted imaging (SWI), Magn Reson Med Sci, 52(3), 612-618. **2**. Cordonnier, C. & van der Flier, Wiesje M., 2011, Brain microbleeds and Alzheimer's disease: innocent observation or key player?, Brain, 134(Pt 2):335-344. **3**. Sturchler-Pierrat, C. et al., 1997, Two amyloid precursor protein transgenic mouse models with Alzheimer disease-like pathology, Proc Natl Acad Sci U S A., 94(24):13287-92.
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