Improved magnetic resonance microimaging of individual amyloid plaques in Alzheimer's transgenic mice

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Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is a leading public health problem. One of the principal pathologies of AD is amyloid plaques, the reduction of which has been identified as a major therapeutic objective. Transgenic mice have been created by inserting human mutations into the mouse genome. These mice form human-like AD plaques and are used extensively to study the biology of AD. Magnetic resonance microimaging (MRMI) has been used to visualize amyloid plaques in both *in vivo* and *ex vivo* transgenic mouse specimens. Due to the intrinsic iron content of plaques, plaques appear dark against normal tissue background on both T_2- and T_2^*-weighted images. In our past experience, spin echo images have performed better than T_2^* weighted images and therefore we adopted this approach. The purpose of these experiments was to assess our ability to increase plaque conspicuity (i.e. contrast-to-noise ratio (CNR)) over our previously validated single spin echo sequence (SSE) (1) by summing multiple spin echoes (MSE) and using multiple spin echo susceptibility weighted imaging (MSE-SWI) (2).

Methods

MRMI experiments were performed with a Unity Inova spectrometer (Varian, Palo Alto, CA) interfaced to a 9.4-T/31-cm horizontal bore magnet. RF transmission and reception was performed with a quadrature surface coil consisting of 1-cm diameter loops. SSE images were acquired with a spin echo sequence described previously (1) with an in-plane resolution of 60 x 60 µm, and a through-plane resolution of 120 µm. The imaging parameters were: TR = 2000 ms; TE = 53 ms; b_w = 30 kHz; *x*, *y*, and *z* matrices of 256 x 96 x 32 with an FOV of 15.36 mm in x, 5.76 mm in y, and 3.84 mm in z. The parameters for the MSE and MSE-SWI sequences were the same except that five echoes were acquired with TE = 38, 53, 68, 83 and 98 ms. The MSE- SWI spin echoes were asymmetric to create 16 ms of T_2^* weighting. Each echo in the MSE and MSE-SWI sequences produced a fully encoded image, which was processed independently, and then summed to increase SNR and CNR. The images were zero-filled to 512 x 192 x 32 giving an apparent in-plane resolution of 30 x 30 µm. The MSE-SWI phase images were high-pass filtered, and then the magnitude images were multiplied by the negative phase mask five times.

Ex vivo imaging was performed on brain of a 19-month-old doubly transgenic (Amyloid pPrecursor pProtein/Presenillin 1 or APP/PS1) mouse which had been fixed and embedded in agar gel.

Results and Discussion

Figures 1a and 1b show images from the SSE sequence, figures 1c and 1d show images from the MSE sequence, and figures 1e and 1f show images from the MSE-SWI sequence. The average CNR of the plaques throughout the image volume in the SSE sequence was 19. Averaging five echoes in the MSE sequence increased the plaque CNR to 31, while the MSE-SWI sequence increased the average CNR to 46. The MSE-SWI sequence also caused the plaques to appear larger due to the T_2^* related blooming effect. Both the MSE and the MSE-SWI sequence increase the plaque CNR over the SSE sequence. We have previously verified by comparisons to histological plaque stains (1) that SSE images accurately capture plaque morphology. The figure illustrates that the MSE sequence accurately captures plaque diameter while plaques bloom on the MSE-SWI sequence. However, plaque conspicuity and CNR are superior with the MSE –SWI sequence. We therefore conclude that of the 3 sequences we compared, if the objective is maximum sensitivity to the presence of individual plaques, then the preferred sequence is MSE-SWI. On the other hand if accurate depiction of plaque diameter is important, then the MSE sequence would be preferred.

References

[1] Jack CR *et al*, *MRM* **52**: 1263 (2004)
[2] Haacke EM *et al*, *MRM* **52**: 612 (2004)

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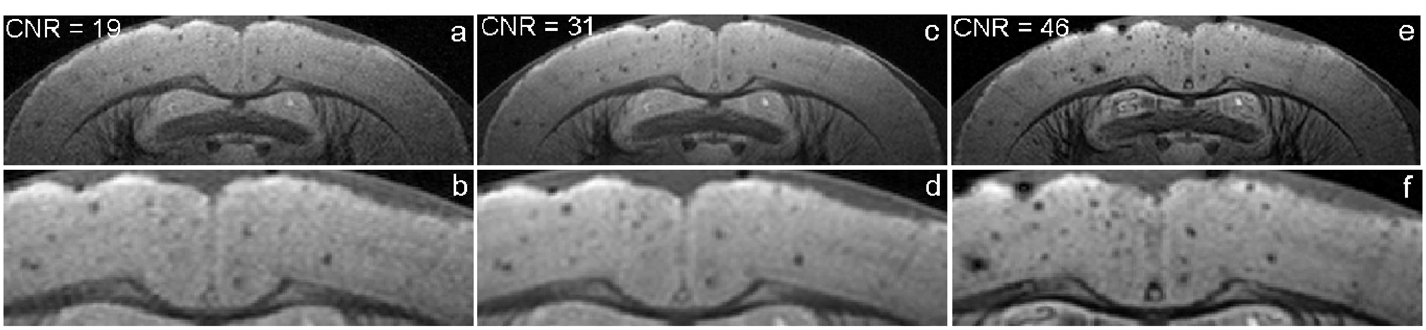

Figure 1. (a) and (b) Single echo T_2-weighted images. (c) and (d) Multi echo T_2-weighted images. (e) and (f) Multi echo SWI images.