# MRI Detection of Early Regional CBV Reduction in Alzheimer's Disease Mouse Model ($APP^{V717F}$)

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**INTRODUCTION** The major physiological, pathological, and cognitive changes reported for AD appear to have a common denominator, which is reflected by the physically distorted cerebro-microvessels and their inability to optimally deliver nutrients to the brain [1]. One of the most important cerebrovascular parameters is the cerebral blood volume (CBV). CBV depends on the microvasculature in specific neural tissue and is coupled to its physiologic state in long term. Accurate and sensitive characterization of regional CBV in AD mouse models has been hampered by a lack of suitable techniques to map CBV with sufficient spatial resolution. In this study, the regional CBV maps in $APP^{V717F}$ transgenic mice were studied with high-resolution MRI using an intravascular contrast agent and steady-state $T_2$-weighted MRI.

**METHODS** 4-mon old $APP^{V717F}$ transgenic mice (N=10) and age-matched wild-type littermate controls (N=12) were used in the study. $APP^{V717F}$ mouse model manifests many of the characteristic neuropathological and behavioral features of Alzheimer's disease (AD) and has proven of great value for studying the pathogenesis of this disorder at the molecular, cellular and behavioral levels [2]. All imaging experiments were performed on a Bruker 9.4 Tesla NMR microimaging system (Bruker NMR, Inc., Billerica, MA). Scout scans were first acquired to position the subsequent $T_2$-weighted images along the standard anatomical orientations in a reproducible manner. The MION bolus (30 mg Fe/kg in 0.2 ml PBS solution) was injected intravenously over a period of 30 s via a femoral vein catheterization while the mouse was inside the magnet. $T_2$-weighted images were acquired with a multi-slice FSE sequence using $TR/TE_{eff}$ = 2000ms/80ms, slice thickness = 0.5 mm, and acquisition matrix = 256 × 256. The FSE sequence offers less susceptibility artifact and also weights the CBV measurement toward the microvasculature [3]. The regional CBV or $\Delta R_2$ maps were computed pixel by pixel as $ln(S_{pre}/S_{post})/TE$ where $S_{pre}$ and $S_{post}$ were the $T_2$-weighted image intensities before and after the contrast agent administration [4]. Note that the CBV estimation is relative here since it is not calibrated to the absolute blood volume fraction in unit of ml/g. Because different brain regions are best visualized in the images along different orientations, CBV maps were acquired for both axial and sagittal orientations. Multi-slice region of interest (ROI) for cerebral cortex and hippocampus were delineated in the seven axial CBV maps and average regional CBV values were computed. Seven other regions were delineated and corresponding average CBV values measured from five central sagittal slices. ROI selections were based from the anatomical SE images and standard mouse neuroanatomy [5]. To minimize the influence of the experimental MION dose error and variation in actual mouse body composition, the regional CBV measurement was normalized to the average CBV in the entire brain. Analyses of regional CBV values in the $APP^{V717F}$ and control mice were performed in a blind manner before the comparison between two groups. The mouse phenotypes were verified.

**RESULTS** CBV or $\Delta R_2$ maps were found to be qualitatively similar in wild-controls and $APP^{V717F}$ mice (Fig. 1). The CBV maps have an in-plane resolution of 100 μm. The CBV distribution was noted heterogeneous even within the same brain region, e.g., in cerebral cortex and olfactory bulb. Superior colliculus, cerebellum, and outer region of the cerebral cortex exhibited high CBV values. In general, the CBV was found to be lower in hippocampal regions except for the hippocampal fissure which is known to be heavily vascularized.

Regional analysis of the multi-slice CBV maps revealed the statistically significant CBV reductions among $APP^{V717F}$ mice in cerebral cortex (-9.29%, p=0.0002), hippocampus (-4.22%, p=0.02), and thalamus (-5.21%, p=003). No significant difference was found in olfactory bulb, pons, midbrain, superior colliculus, medulla, and cerebellum (see table).

In summary, the high-resolution CBV mapping shows reduced cerebral blood volume in selected regions in young $APP^{V717F}$ mice at resting state when compared to the age-matched wild-type controls, indicating an early change of microvasculature in cerebral cortex, hippocampus, and thalamus in this AD mouse model in addition to impaired cerebrovascular autoregulation and reactivity [6,7] and volume reduction of dentate gyrus [8] recently reported by others. Such vascular change may be a key factor in the complex interplay of behavioral deficits, plaque formation, abnormal metabolism, hemodynamics, and tissue volumetric changes, which remains to be explored in the future study.

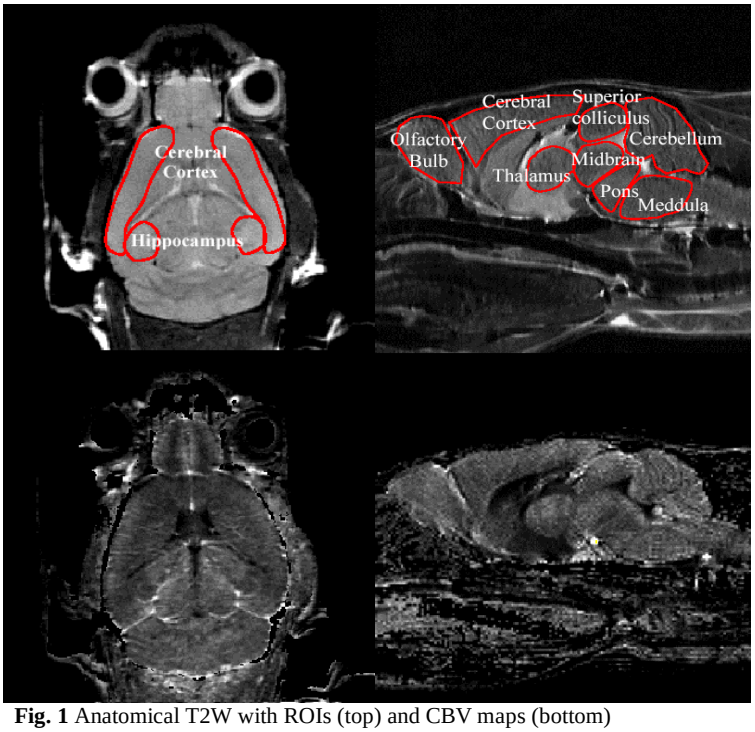


**Fig. 1** Anatomical T2W with ROIs (top) and CBV maps (bottom)

| | *Normalized CBV Wild-type controls (N=12)* | *Normalized CBV $APP^{V717F}$ (N=10)* | *Percentage Difference (%)* | *p value* |
|---|---|---|---|---|
| **Cerebral cortex** | 1.03±0.04 | 0.94±0.06 | 9.29 | 0.0002 |
| **Hippocampus** | 0.801±0.03 | 0.767±0.03 | 4.22 | 0.02 |
| **Thalamus** | 1.10±0.05 | 1.05±0.06 | 5.21 | 0.03 |
| **Olfactory bulb** | 1.07±0.02 | 1.10±0.04 | -0.7 | NS |
| **Superior colliculus** | 1.31±0.06 | 1.30±0.10 | 0.54 | NS |
| **Cerebellum** | 1.17±0.05 | 1.2±0.04 | -1.97 | NS |
| **Meddula** | 1.11±0.03 | 1.14±0.07 | -2.59 | NS |
| **Pons** | 0.86±0.05 | 0.87±0.05 | -1.24 | NS |
| **Midbrain** | 1.14±0.06 | 1.12±0.05 | 1.56 | NS |

**REFERENCES** **1**.Farkas E et al. Prog Neurobiol. 64(6):575, 2001. **2**.Games D et al. Nature 373(6514):523, 1995. **3**. Boxerman JL et al. MRM 34:555, 1995. **4**.Wu EX et al. MRM 49:765, 2003. **5**. Paxinos G & Franklin KBJ, Academic Press, 2001. **6**. Niwa K et al. Am J Physiol Heart Circ Physiol 283:315, 2002. **7**. Mueggler T et al. J Neuroscience 23:8231, 2003. **8**. Redwine JM et al. PNAS 100:1381, 2003.