Magnetic Resonance Microscopic Angiography Visualization of Abnormal Microvasculature in a Transgenic Mouse Model of Huntington's Disease

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Synopsis
The underlying mechanisms of neurodegenerative disease are still unclear. However, the cerebral microcirculation may play an important role. This study aimed to explore the microvasculature in a transgenic mouse model of Huntington's disease using newly developed microscopy MRA.

Introduction
Huntington's disease (HD) is a genetic brain disease characterized by gradual onset and progression motor, cognitive and psychiatric symptoms (1). The HD mutation causes progressive neurodegeneration and death usually occurs within one or two decades after first occurrence of symptoms. Previous MRI studies using functional MRI and diffusion tensor imaging have improved understanding of striatal atrophy and cortical dysfunction in HD mutation (2). However, the underlying mechanisms for the neurodegeneration in HD remain obscure. Our hypothesis is that the brain atrophy and dysfunction of HD may attribute to the abnormal cerebral microcirculation. To the best of our knowledge, no study reports the alteration in microvasculature of HD so far. A novel technique, microscopy magnetic resonance angiography (3DΔR2-mMRA), has been recently proposed to study rat cerebral microvasculature, and it can be used to both visualize the neuromicrovascular architecture and provide information on the physiological status of the microvascular cerebral blood volume (CBV) (3). The first purpose of this study was to establish 3DΔR2-mMRA for visualizing microvessel from rat to mouse brain, and the second purpose was to apply this technique to investigate the change of cerebromicrovasculature in a transgenic mouse model of HD.

Material and Methods
All images were performed on a 4.7-T Biospec 47/40 MR scanner with an active shielding gradient. Male R6/2 mice and littermate controls were originally obtained from Jackson Laboratories (Bar Harbor, ME, USA), and mated to female control mice (B6CBAFI/J). Offspring were identified by the PCR phenotyping technique of genotyping DNA extracted from tail tissue. In total, five transgenic mice and five wild-type (WT) littermate control mice were used in this study. The mice were initially anesthetized with 5% isoflurane at 1L/min air flow. When fully anesthetized, the animal was placed in a prone position and fitted with a custom-designed head holder inside the magnet. Isoflurane was then maintained with 1 % at 1L/min air flow throughout the experiments. Images were acquired using a 72-mm birdcage transmitter coil and a separate quadrature surface coil for signal detection. To determine ΔR_2, T2-weighted images (T2WI) were performed before and after an injection of iron oxide (Resovist, Schering AG, Berlin, Germany) at a dose of 30 mg Fe/kg. The post-contrast image acquisition was delayed by 1-2 minutes for ensuring a steady state distribution of contrast agent in the vascular network. Contrast agent was injected into mice via tail vein. T2WI were acquired using 3D RARE sequence with a TR of 1500 ms, a TEeff of 84 ms, ETL of 32, 6 averages, FOV = 2 cm × 1.8 cm × 1 cm, acquisition matrix = 256×192×96 (zero-padded to 512×384×192). The image resolution in three directions was 39.06, 46.87, and 52.08 μm. ΔR_2 map was calculated pixel-by-pixel using an in-house software written by Matlab (MathWorks, Natick, MA, USA). 3D view of microvasculature was constructed with 3D ΔR2 map using a volume-rendering utility (TGS, Amira, San Diego, CA).

Results and Discussion
The temporal change of T2WI and 3D microangiography in WT and HD mice brains is shown in Fig. 1A and 1B, respectively. T2WI demonstrates the brain structure, in which no change can be found in WT mice brain, while the ventricular enlargement as the disease progression was observed in HD brain which likely reflected atrophy of paraventricular brain regions. Intracortical and deep subcortical small-vessel structure in mouse brain can be delineated by 3D microangiography. WT brain shows the consistence of cerebral microvasculature from age of 7 to 12 weeks, while many and inorganized microvessels were observed in cortical and striatal region of HD mutation brain as the disease progression which was supported by the microvessel extraction (Fig. 2). In addition to visualizing the alteration of microvascular structure, we further measured CBV in cortical region (Fig. 3). No significant change of CBV was observed in WT, while HD brain showed the gradually increase of CBV as the disease progression. These results suggest that abnormal microcirculation may contribute to the pathogenesis of Huntington's disease and often precedes the onset of clinical symptoms.

Conclusion
The current study using high-resolution microscopy MRA demonstrates that the abnormal microcirculation observed in HD brain might provide a new strategy to investigate the neurodegenerative disease.

Reference
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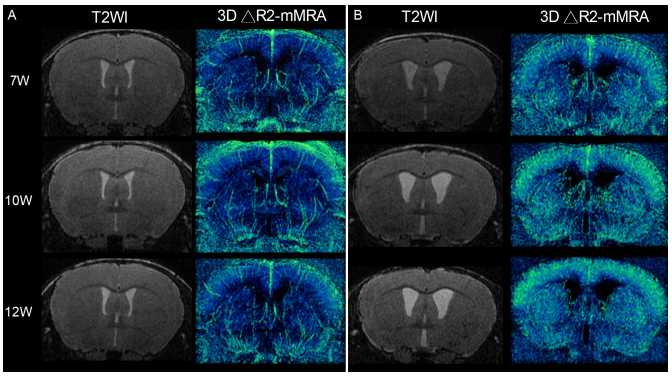

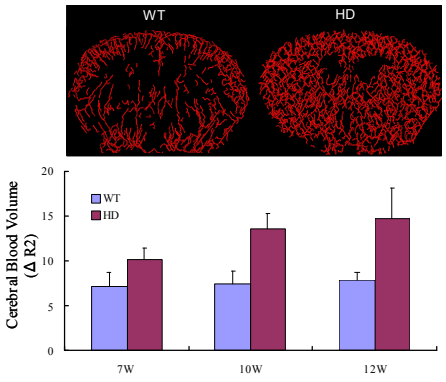

Fig. 1. Temporal change of T2WI and 3D microangiography in (A) WT and (B) HD mice brains.
Fig. 2. The cerebral microvessel extraction of WT and HD at 12 weeks from 3DΔR2-mMRA using Tree-structure Extraction Algorithm (Upper right).
Fig. 3. Quantitative analysis of ΔR2 in cortical region of WT and HD brains (Lower right).