Quantitative assessment of axonal transport integrity in the mouse brain *in vivo* using MEMRI at 9.4 T

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INTRODUCTION

Increasing evidence suggests that axonal transport deficits play a key role in the impairment of neuronal viability and in the development and progression of neurodegenerative diseases such as Alzheimer's disease [1]. Although axonal transport rates were assessed *in vivo* using T_1-weighed MRI [2], the full description of quantitative measurements of axonal transport integrity *in vivo* has not been reported to date. The purpose of this study was to develop a fast MRI technique that provides T_1 values to investigate axonal transport in the brain *in vivo* in a quantitative manner using manganese-enhanced MRI (MEMRI) [3]. We examined the Mn^{2+} uptake and transport through microtubules of the olfactory system of the mouse brain using odor stimulation.

METHODS

Fourteen week old C57/Bl6 mice were initially anesthetized with 5% isoflurane in 50% oxygen and 50% air mixture. Five minutes after the induction, $MnCl_2$ solution (USB Corp, Cleveland OH, USA) was administered into the nasal cavity of the mice (1 M, 4-5 μl). The animals were allowed to wake up in the cage and the amyl acetate odor was presented for 10 min. Animals were the anesthetized with 1.5 – 2% isoflurane and placed in a plastic holder with a nose cone in the prone position for MR imaging. Body temperature of animals was maintained to ~37 ± 1 ^{o}C using a circulating water blanket.

All measurements were performed with a Varian 9.4 T system (Varian, Palo Alto, CA) with 12 cm diameter gradient sets. MR images were acquired using a custom built 7 mm single loop RF coil that was inductively coupled to a driving circuit. Magnetic field homogeneity of the olfactory bulb was optimized using manual adjustment of the first and the second order shim currents. Time courses of manganese enhanced MR signals were measured using a T_1-weighted sequence (multi-slice gradient echo sequence, TR = 100 ms, TE = 2.9 ms, flip angle = 70^{o}, slice thickness = 400 μm, FOV = 1.5 cm, matrix = 128 x 128, number of slices = 7, NEX = 4, and scan time = 51 s). T_1 maps were acquired using a sequence based on the inversion recovery TruFISP sequence [4] with multi slice implementation at multiple time points (TR = 5.6 ms, TE = 2.8 ms, FOV = 1.6 cm, slice thickness = 400 μm, number of slices = 3, matrix = 128 x 128, 16 inversion times, NEX = 2, and scan time = 5 min).

RESULTS AND DISCUSSION

Figure 1 shows high resolution T_1-weighted images acquired after $MnCl_2$ administration and olfactory stimulation with amyl acetate. Preferential accumulation of manganese was observed at specific regions in the olfactory bulb responding to the stimulation by amyl acetate, which is consistent with previous studies. T_1 measurement was performed at 122, 160, and 174 minutes after manganese administration. Fig. 1C shows the corresponding T_1 map of Fig. 1A and 1B at time 122 min. T_1 values measures from the central regions of enhancing area (black arrow head at Fig. 1B) were 0.94, 0.88, and 0.83 s at time points of 122, 160, and 174 min, respectively.

Previous study has shown a time dependent manganese accumulation at olfactory bulbs through a time course analysis of T_1 weighted images [2]. However, using T_1-weighted images alone cannot provide an accurate estimation of manganese accumulation in the brain tissue since the T_1-weighting depends on flip angle variations due to RF inhomgeneity and inherent T_1 variations of the brain tissue. Current preliminary study demonstrates the feasibility of fast, high resolution T_1 measurements to follow the time course of manganese accumulation at the olfactory bulbs, which eliminates the dependence on B_1 and T1 variations. This technique will be a valuable tool to characterize axonal transport deficits in transgenic mouse models of neurodegenerative and neurological diseases.

REFERENCES

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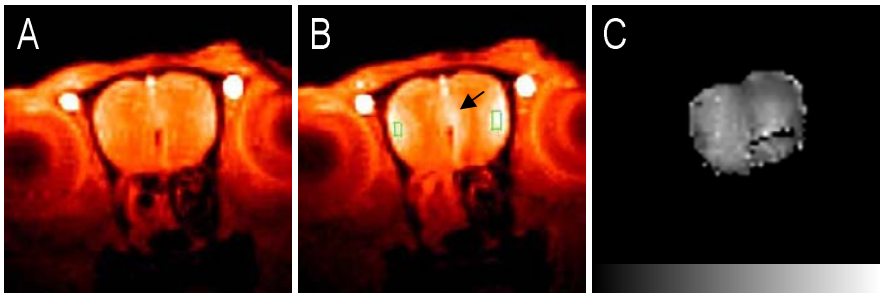

Fig. 1. T_1-weighted MR images acquired at (A) 88 min and (B) 172 min after $MnCl_2$ administration. (C) T_1 map of mouse olfactory bulbs at time 122 min. Gray bar indicates the T_1 values from 0.2 to 2 s.

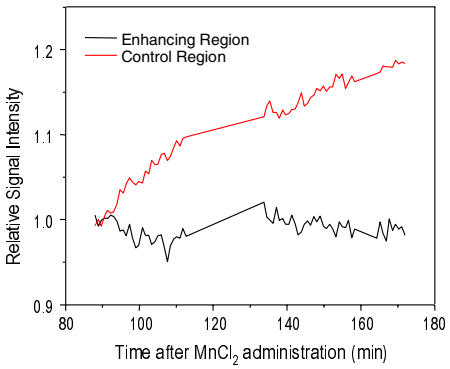

Fig. 2. Time course of relative signal intensity of T_1 weighted images measured from the contrast enhnacing region (green rectangles in Fig 1B) and adjacent non-enhancing region.