In vivo Manganese-enhanced MRI of Retinotopic Mapping in Superior Colliculus

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INTRODUCTION: The superior colliculus (SC) is a dome-shaped subcortical laminar structure in the mammalian midbrain, whose superficial layers receive visual information from the retina in a topological order (1-2). Despite the increasing number of studies investigating the retinotopic projection in visual brain development and disorders (2-4), *in vivo*, high-resolution 3D mapping of retinotopic organization in the subcortical brain nuclei has not yet been available. Mn^{2+} has been increasingly used as a T_1-weighted contrast agent for neuronal tract tracing (5-6) and functional brain mapping at lamina levels (7). In this study, we explore the capability of 3D Mn-enhanced MRI (MEMRI) for *in vivo* retinotopic mapping of the rat SC upon partial transection of the intraorbital optic nerve.

MATERIALS AND METHODS: Animal Preparation: Sprague-Dawley rats (200-250 g, N=15) were divided into 2 groups. In Group 1 (n=8), the superior region of the right intraorbital optic nerve was partially transected at about 2 mm from the eye. In Group 2 (n=7), the right optic nerve was partially transected at the same distance from the eye but in other regions. One week after surgery, $MnCl_2$ solution (3μL, 50mM) was injected intravitreally into both eyes of each group. MEMRI was performed 1 day after Mn^{2+} administration. Throughout the experiment, the left optic nerve was not transected and the Mn^{2+} enhancement pattern in right SC served as an internal control. **MRI Protocol:** All MRI measurements were acquired utilizing the 7 T Bruker scanner using a receive-only surface coil. 3D spin-echo T_1-weighted (T1W) imaging was acquired covering the entire visual pathway, with TR/TE = 250/6.7ms, FOV = 32x32x16mm^3, acquisition resolution = 200x200x200μm^3, RARE factor = 4 and number of averages = 4. Total scan time was 40 mins. **Data Analysis:** Maximum intensity projection (MIP) was performed onto the 3D T1W images after segmenting the visual pathway from the retina to the subcortex in both hemispheres. The apparent volume of Mn^{2+} enhancement in left SC was quantified by selecting pixels with signal intensities greater than (mean - 2 standard deviations) of the signal intensity in right control SC using ImageJ v1.42q. The signal intensities of Mn^{2+} enhancement in the subcortical visual nuclei, including SC and lateral geniculate nuclei (LGN) were also measured. Values between contralateral SC and LGN, and between two halves of left SC were compared using two-tailed paired t-tests. Results were considered significant when $p<0.05$.

RESULTS: In the MIP image in Fig. 1a, intravitreal Mn^{2+} injection into the left control eye resulted in enhancements in the entire superficial layers of the contralateral SC in consistency with previous reports (5-6), whereas in the contralateral right eye 1 week after partial transection, a clear border was observed separating the lateral and medial regions of left SC in Group 1 (Figs.1a-b), and other regions of left SC in Group 2 (Figs. 1c-d). The apparent volume of Mn^{2+} enhancement in left SC was significantly smaller than the right SC in both groups to similar extents ($p<0.001$) (Fig. 2). On the other hand, all animals in Group 1 exhibited a significantly lower signal intensity in the left lateral SC compared to left medial SC and right control SC by 16%±6% and 28%±7% respectively ($p<0.001$) (Fig. 3). In Group 2, the darker half of left SC had a lower intensity than the brighter half of left SC and the right SC by 15%±4% and 30%±5% respectively (Fig. 3). The signal intensities in the left medial SC in Group 1 and the brighter half of left SC in Group 2 were also significantly lower than the right SC by 14%±7% and 18±7% respectively ($p<0.01$), whereas the left LGN had a respective 19±10% and 22%±4% of signal drop compared to the right control LGN in both groups ($p<0.01$) (Fig. 1).

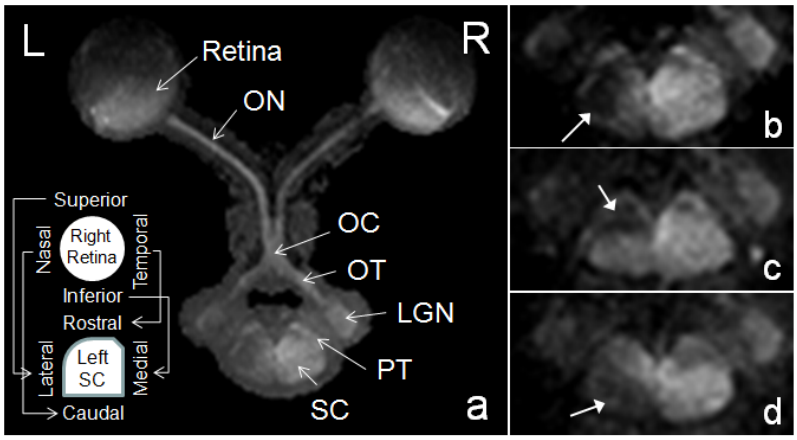

Fig. 1: (a) MIP of the visual pathway from retina to subcortex at 1 week after partial transection of the right superior optic nerve and 1 day after intravitreal Mn^{2+} injection in Group 1. Inset illustrates the graphical representation of retinotopic projection from right retina to left SC; (b-d) Expanded views of the SC showed the substantial reduction in Mn^{2+} enhancement in the lateral region of the left SC in Group 1 (b) and other regions in Group 2 (c-d) as indicated by the solid arrows. Note the clear border separating two halves of the left SC. Note also the hypointensity in the left LGN. (ON: optic nerve; OC: optic chiasm; OT: optic tract; LGN: lateral geniculate nucleus; PT: pretectum.)

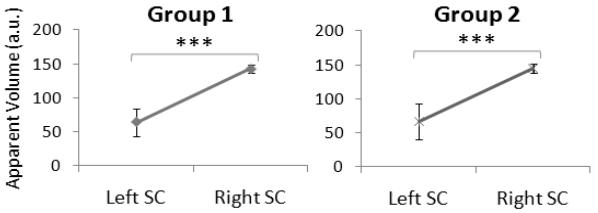

Fig. 2: Comparison of apparent volumes of Mn^{2+} enhancement in the left and right SC in both groups (Two-tailed paired t-test, *p<0.05;**p<0.01;***p<0.001).

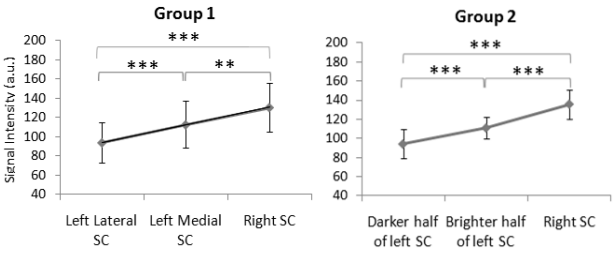

Fig. 3: Comparison of T1W signal intensities among the darker and brighter halves of left SC, and the entire right SC in both groups (Two-tailed paired t-test, *p<0.05;**p<0.01;***p<0.001).

DISCUSSIONS AND CONCLUSION: Previous histological and electrophysiological studies showed that the retinal ganglion cell axons emanating from superior, inferior, nasal and temporal retina project respectively to the contralateral lateral, medial, caudal and rostral SC in rodents (1-2) [Fig. 1a (inset)]. While this topological pattern is preserved in the intraorbital region of the optic nerve (8), it was shown that partial transection of the superior intraorbital optic nerve led to primary injury predominantly in the superior but not inferior retina and optic nerve (9). The results of this study demonstrated the feasibility of high-resolution MEMRI for *in vivo*, 3D mapping of retinotopic projections in the SC upon reduced anterograde axonal transport of Mn^{2+} ions at sites of partial transections in the anterior visual pathways. Results in Group 1 ensured the consistency of hypointensity in the left lateral SC upon superior intraorbital optic nerve transection, whereas the clear border separating two halves of the left SC in both groups indicated the precise topographic projections of the retinocollicular axons in correspondence to the edge of the partial transection in the optic nerve. Whether the lower intensity in the brighter half of left SC than right SC was related to secondary degeneration (9) in both groups remained to be elucidated. Future MEMRI studies are envisioned that measure the retinotopic changes in normal development, disease, plasticity and therapy in longitudinal studies.

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