

In Vivo Magnetic Resonance Imaging of Activity-dependent Neural Progenitor Cell Migration

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Target audience: Neuroscientists, stem cell researchers, and researchers in the fields of cellular MR imaging and tracking

Purpose: To use in situ MRI cell labeling and serial monitoring to investigate the question of whether changes in levels of olfactory sensory can affect the speed of NPCs as they travel from the subventricular zone (SVZ) to the olfactory bulb (OB) as well as their cellular fates in the OB.

Methods: 3-week old Sprague-Dawley rats (Charles River Laboratories, Inc., Wilmington, MA) were subjected to reversible unilateral naris occlusion. After 3 weeks, the animals were stereotactically injected with 20 μ L MPIOs (average diameter of 1.63 μ m, Bangs Laboratories, IN Fishers) into the side of the occluded nostril. The injection coordinates into the lateral ventricle were 2 mm caudal and 2 mm medial to bregma, and 3 mm ventral from the dura. MPIO injections were also performed in 6-week old rats as a control group. MRI data was acquired on an 11.7 T animal MRI system (30 cm 11.7 T horizontal magnet, Magnex Scientific, Oxford, England, MRI Electronics, Bruker Biospin, Billerica, MA, and 12 cm integrated gradient shim system (Resonance Research Inc, Billerica, MA) using a custom built volume transmit coil and a custom built, 2.5 cm diameter, receive-only surface-coil. Flash 3D gradient echo sequences were used for all MRI acquisitions with the following parameters: FOV 2.56 cm³ or 1.92 cm², matrix size 256³ (100 μ m or 75 μ m isotropic resolution), 12.5 kHz bandwidth, TE 8 ms, and TR 25 ms. MRI was performed at 4-6 and 22-24 hour post-injection. The migration rate was calculated by measuring the distance that cells travel in a given period between the first and second MRI session.

Results: Figure 1 shows marked reduction of OB volume after 3 weeks of unilateral naris occlusion as expected. Following the injection of MPIO, labeled cells are detectable as dark spot due to signal loss in T₂*-weighted images. Within 4 hours post injection, MPIOs could be detected with MRI in the early RMS (figure 2 A and B). Previous works by Shapiro et al. and Sumner et al. revealed that migration of contrast signal along RMS requires cell migration and that MPIOs could label all cell types.^{1,3} Therefore, it is reasonable to state that migrating cells traveled along RMS and reached the entrance of OB as early as 24 hours as shown in figure 2 B and D. Migration rate of NPC in the control and naris-occluded rats were 120 \pm 10 and 90 \pm 5 μ m/h, respectively (figure 2E).

Discussion: In this work, we performed an injection of MPIO for MRI labeling of endogenous NPCs in a rat model of sensory activity deprivation. An Injection volume of 20 μ L MPIOs solution was found to be optimum for achieving an efficient labeling. In the control animal, our observation is in good agreement with recent work published by other laboratories that cells can migrate along RMS at the top speed of 120 μ m/h.^{3,4} Interestingly, there was a modest, but significant, decrease of the speed of cell migrating into OB in naris-occluded rats. It has been shown that post natal naris occlusion led to significant loss of interneurons and survival of precursor cells in OB due to declining sensory input. Thus, it is possible that reduction of activity could suppress cellular turnover to such extent that results in slower rate of precursor cell migration. Cellular fate and distribution within OB is currently being investigated and will be discussed.

Conclusion: By using MRI, we demonstrate that alteration of olfactory sensory input can affect cell migration rate in the brain, although the underlying mechanism of this process is unclear. Previously, NPCs have been shown to migrate from SVZ to sites of brain damage where they are thought to promote recovery and replenish local neurons.^{4,5} Our observation supports a growing interest in modulating endogenous stem-progenitor cells for the potential use in regenerative therapies.

References: [1] Sumner J. P. et al., *Neuroimage* 44: 671-678 (2009) [2] Nieman, B. J. et al., *Neuroimage* 50: 456-464 (2010) [3] Granot, D. et al., *Neuroimage* 57: 817-824 (2011) [4] Arvidsson, A. et al., *Nat Med* 8: 936-970 (2002) [5] Tattersfield, A. S. et al., *Neuroscience* 127:319-332 (2004)

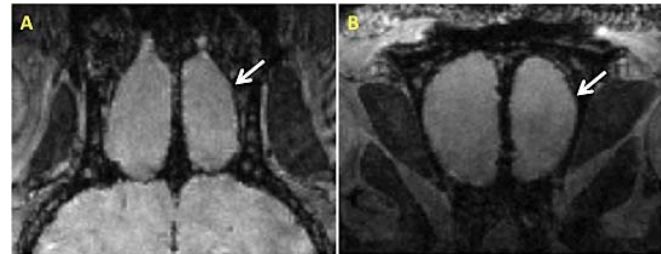


Figure 1. Coronal (A) and axial (B) views of MR images of rat OB after 3-week naris occlusion. Arrows indicate shrinkage of the right OB in comparison with the right OB.

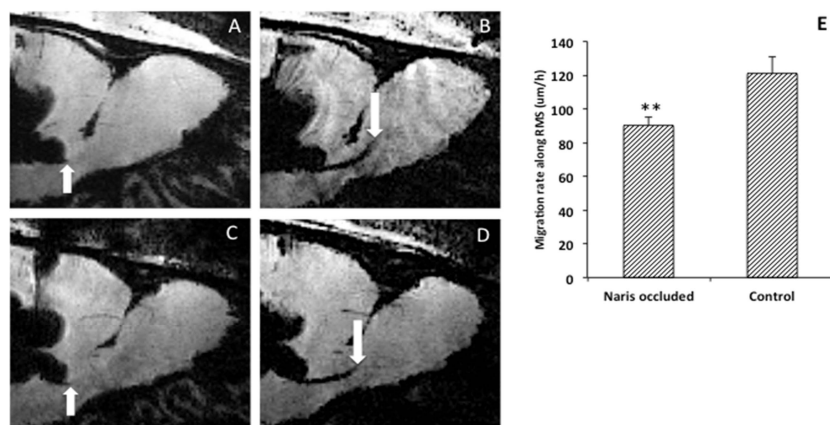


Figure 2. MR images of the brains of control rat (A, B) and naris-occluded rat (C, D) after 4-6 h (A, C) and 22-24 h (B, D) of MPIO injection into lateral ventricles. Figure 2E shows rates of cell migration (N=5).