Migration Dynamics of Neural Progenitor Cells Revealed by MRI

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Introduction

Neural progenitor cells (NPCs) are produced throughout life in the subventricular zone (SVZ) and migrate a surprisingly long distance to the olfactory bulb (OB) where they replace interneurons. Under conditions of disease, they are also capable of migrating to sites of damage, suggesting they might be useful in novel cell-based therapies. The migration capabilities of NPCs are therefore of particular significance. In this study, we evaluate the speed of migration of these cells en route to the OB and their pattern of distribution upon arrival using injections of micron-sized particles of iron-oxide (MPIOs) followed by longitudinal MRI [1,2].

Methods

MPIOs (1-2x10^6) were stereotaxically injected into the anterior region of the SVZ of female ICR mice under isoflurane anesthesia. For evaluation of initial migration speed, mice were image imaged on day 0 (immediately after surgery) and then on days 1 and 2. For evaluation of RMS and OB distribution over longer times, mice were imaged on days 0, 4, 7, and 21. All images were acquired on a 7.0T magnet equipped with a Bruker console using a multiple gradient-echo sequence (TR = 40 ms, TE = 4.0, 8.3 ms, 12º excitation). For analysis, hypointense voxels were segmented computationally using the contralateral bulb as an intensity reference. For this purpose, images were flipped in the left-right direction and then registered nonlinearly to the original image. Intensity differences were then evaluated voxel-by-voxel and thresholded by the false discovery rate (FDR).

Results

The initial migration of NPCs in the RMS was very rapid. By day 1, contrast was already evident over most of the RMS (Fig 1), suggesting a migration speed of as fast as 109 µm/hr (average of N=3 mice). By day 2, the start of NPC distribution through the OB was observed, but migration speeds had slowed (~46 µm/hr). For validation, particles were counted in axial sections and their distribution plotted as a function of distance from the injection sight.

Evaluation of the distribution through the OB over the course of 3 weeks shows a slow evolution of labeled cell location, primarily in the parasagittal plane running through the medial OB (Fig 2). Immunohistochemistry in the OB revealed that most MPIO+ cells were neuronal, although an increasing number of particles were also observed in phagocytic cells (Fig 3).

Discussion and Conclusions

NPCs can migrate at as fast as 109 µm/hr on their journey to the OB, hence completing the trip in less than 2 days. Their distribution through the OB is much slower and progresses over the course of several weeks. Evaluation of migratory potential to sites of injury will be of particular interest in considering the therapeutic potential of these cells.

Acknowledgements

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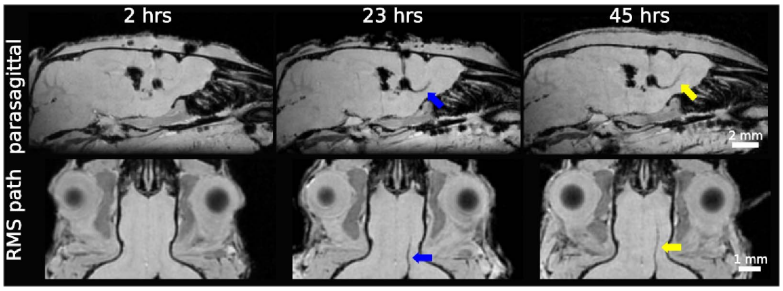

Figure 1: RMS Migration. An individual mouse imaged on consecutive days shows rapid migration along the RMS on day 1 (blue arrows) and the start of OB distribution by day 2 (yellow arrows).

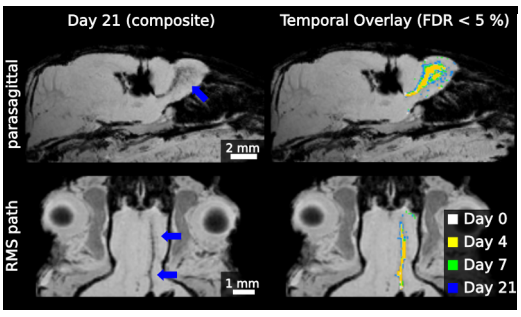

Figure 2: Distribution in the OB. Over the course of 3 weeks, labeled cells distribute in the OB (left column, blue arrows). At right, overlays of hyointense regions at days 0, 4, 7, and 21 are shown.

[1] Shapiro EM et al NeuroImage 2006; 32:1150-7.
[2] Shyu HY et al. Proc 16th ISMRM 2007; 1678.

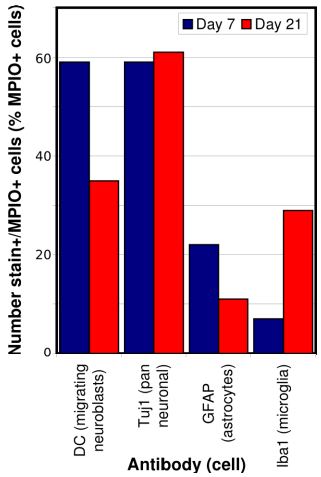

Figure 3: MPIO+ cells in the OB. Most MPIO+ cells that reach the OB are neuronal. An increasing number of particles are also seen in microglia.