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REVIEW

# *In vivo* imaging of endogenous neural stem cells in the adult brain

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## Abstract

The discovery of endogenous neural stem cells (eNSCs) in the adult mammalian brain with their ability to self-renew and differentiate into functional neurons, astrocytes and oligodendrocytes has raised the hope for novel therapies of neurological diseases. Experimentally, those eNSCs can be mobilized *in vivo*, enhancing regeneration and accelerating functional recovery after, *e.g.,* focal cerebral ischemia, thus constituting a most promising approach in stem cell research. In order to translate those current experimental approaches into a clinical setting in the future, non-invasive imaging methods are required to monitor eNSC activation in a longitudinal and intra-individual manner. As yet, imaging protocols to assess eNSC mobilization non-invasively in the live brain remain scarce, but considerable progress has been made in this field in recent years. This review summarizes and discusses the current imaging modalities suitable to monitor eNSCs in individual experimental animals over time, including optical imaging, magnetic resonance tomography and-spectroscopy, as well as positron emission tomography (PET). Special emphasis is put on the potential of each imaging method for a possible clinical translation, and on the specificity of the signal obtained. PET-imaging with the radiotracer 3′-deoxy-3′-[$^{18}$F]fluoro-L-thymidine in particular constitutes a modality with excellent potential for clinical translation but low specificity; however, concomitant imaging of neuroinflammation is feasible and increases its specificity. The non-invasive imaging strategies presented here allow for the exploitation of novel treatment strategies based upon the regenerative potential of eNSCs, and will help to facilitate a translation into the clinical setting.

**Key words:** Neural stem cells; Positron emission tomography; Magnetic resonance imaging; 3′-deoxy-3′-[$^{18}$F]fluoro-L-thymidine; [$^{11}$C]PK11195



**Core tip:** Endogenous neural stem cells (eNSCs) in the adult mammalian brain can be mobilized by, *e.g.*, pharmacological methods to facilitate regeneration and enhance functional recovery in neurological disease. In order to translate experimental approaches into the clinical setting, non-invasive imaging of eNSCs is required to monitor their fate *in vivo*. This review summarizes current imaging modalities suitable to monitor eNSCs in individual experimental animals over time, including optical imaging, magnetic resonance tomography and-spectroscopy, as well as Positron-Emission-Tomography, placing emphasis on the specificity of the signal obtained, as well as on their potential for clinical translation.

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## NEURAL STEM CELLS IN THE ADULT MAMMALIAN BRAIN

The discovery of neural stem cells (NSCs) in the adult brain and their ability to self-renew and differentiate into tissue-appropriate, functional cell types has raised intense scientific interest and the hope for radical new therapies of neurological diseases. Altman *et al*[1] first detected the ability of the adult mammalian brain to generate new neurons, and their work was followed up by Kaplan *et al*[2]. Using radioactive thymidine to label all dividing cells and histological examination of postmortem brains, they found labeled neurons. This proved that new neurons in the adult brain can be generated following cell division. After those pioneer studies focusing on neurogenesis, later studies aimed to detect the immature precursor cells capable of differentiating into all three cell fates of the central nervous system (CNS): neurons, astrocytes and oligodendrocytes. Several biomarkers have been suggested to identify those undifferentiated stem cells in the brain, the first one being the intermediate filament nestin (neuroepithelial stem cell intermediate filament[3]). Subsequently, NSCs were characterized in the developing and in the postnatal/adult mammalian brain[4-11]. More biomarkers were consecutively identified including *Sox2*, *Shh* pathway components, PDGF, EGFR, GFAP, Hes3, Hes5, Musashi, and CD133[5,12-22]. However, since no single marker has yet been identified to unambiguously distinguish NSCs from somatic cells, co-stainings are usually required to comprehensively characterize them. It is now well accepted that endogenous NSCs (eNSCs) persist in the adult mammalian brain in at least two distinct regions, the subventricular zone, lining the lateral ventricles, and the dentate gyrus of the hippocampus[23,24].

Insults to the CNS such as cerebral ischemia or neurodegenerative disease result in a mobilization of eNSCs and their migration towards the compromised areas[25-29], constituting a physiological regenerative response of the brain. However, in most cases the intrinsic regenerative response of eNSCs is obviously not sufficient to lead to functional recovery. Experimentally, it has been shown that eNSCs can be mobilized pharmacologically for therapeutic purposes. Early studies showed that activating the tyrosine kinase receptors for fibroblast growth factor 2 and epithelial growth factor on eNSCs by introducing those growth factors into the lateral cerebral ventricle of experimental animals stimulates the proliferation of eNSCs *in vivo*[30,31]. Ligands for these receptors also show benefit in animal models of cerebral ischemia, where growth factor-induced eNSC mobilization is associated with enhanced functional recovery from motor deficits[32,33]. Recently, several other drugs have been identified to mobilize eNSCs in the naïve and in the injured rodent brain, including Notch-ligands[13], angiopoietin 2[14], the neural cell adhesion molecule mimetic peptide FG Loop[34], and aromatic-turmerone[35]. Enhancing this (physiological) mobilization of eNSCs by pharmacological intervention leads to an improvement of neurological function after, *e.g.,* cerebral ischemia[13,32,33]. To convey these regenerative effects, it seems that the differentiation of eNSCs into mature neurons that functionally integrate into the damaged circuitry-previously thought to be required for regeneration-only plays a minor role[36]. Rather, eNSCs secrete trophic factors supporting neuroprotection such as glial-derived neurotrophic factor, vascular endothelial growth factor, or *Shh*[13,37]. Other regenerative processes induced by NSCs include remyelination, angiogenesis, remodeling, and immunomodulation[38,39]. Since treatments based on the transplantation of stem cells harbor several disadvantages including poor long-term cell survival, a lack of integration into the host circuitry, immune reactions against the transplants, and limited availability of appropriate cells[40], mobilizing the endogenous neural stem cell niche for therapeutic purposes constitutes a most promising approach in stem cell research.

## IMAGING ENDOGENOUS NEURAL STEM CELLS *IN VIVO*

Developing strategies to mobilize the endogenous NSC niche *in vivo*, with the aim to later translate them into clinical applications, creates the need for *in vivo* imaging technology to monitor those interventions. Imaging techniques should be non-invasive, so they can be applied repetitively in the same individual in a longitudinal fashion, and thus track quantity and localization of endogenous NSC over any period of time. While considerable progress has been made in recent years to track transplanted, pre-labeled cells[41-47], the detection of endogenous NSCs in the living brain remains elusive. Current approaches to image eNSCs *in vivo* include (1) the use of transgenic animals whose eNSCs exhibit certain imaging properties; (2) labeling eNSCs *in vivo* by injecting a labeling substance into the brain; or (3) imaging some intrinsic and putative unique property of eNSCs with a tailored imaging assay.

Transgenic animals expressing a fluorescent or bioluminescent protein under the control of a stem cell-characteristic promoter such as nestin or doublecortin render their eNSCs detectable by optical imaging techniques[48-52]. Under ideal conditions, optical imaging can specifically detect clusters of about $10^3$ cells *in vivo*, but its sensitivity is limited by the relatively poor spatial resolution with shallow tissue penetration[53]. Moreover, the need for transgenic mice limits the potential applications of optical imaging and prohibits its translation into a clinical setting.

In the attempt to (specifically) label eNSCs *in vivo*, various methods have been suggested. Labels can be micro-injected directly into (or close to) the neurogenic

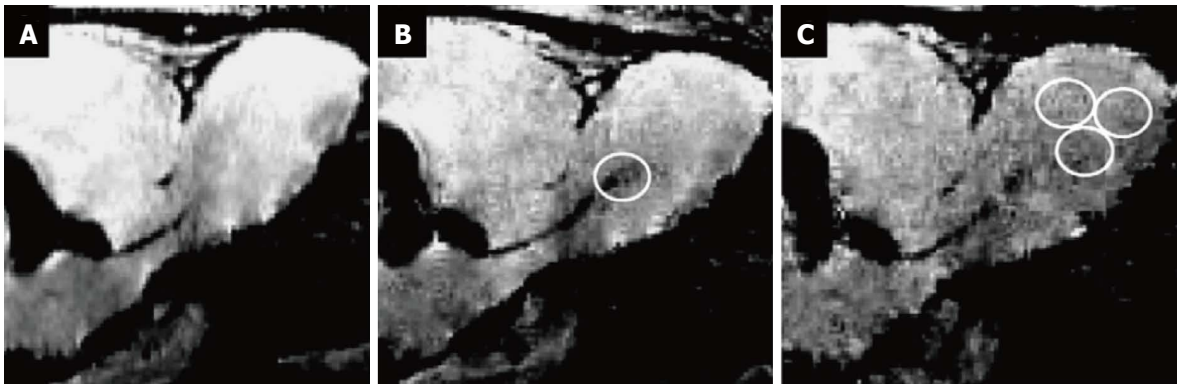


**Figure 1 Monitoring the migration of endogenous neural stem cell labeled with iron oxide particles in the rat brain *in vivo*, using magnetic resonance imaging.** Migrating cells were imaged 1 d (A), 3 d (B), and 8 d (C) after labeling, migrating from the subventricular zone (left in the sagittal images) to the olfactory bulb (on the right). White circles surround migrating cells. Granot *et al*[54], with permission. MRI: Magnetic resonance imaging.

niches, or they can be coupled to a vector in order to specifically target certain cells. Direct injection of a paramagnetic label such as small particles of iron oxide allows for cell detection using magnetic resonance imaging (MRI) with excellent spatial resolution on the single cell level (Figure 1)[54-59]. However, this type of labeling is neither specific for a certain cell type, nor does it reflect cell viability, as only the particles themselves are visualized[53]. Moreover, directly injecting iron oxide in *e.g.,* the lateral ventricles of the brain results in image distortion in the region of injection, allowing only for the detection of cells migrating away from the injection site[54,57,58]. A more specific *in vivo* labeling approach is achieved by attaching an imaging label to a retro- or lentiviral vector, thus targeting proliferating cells in particular. This has been shown to be effective for optical imaging techniques after introduction of firefly luciferase[60,61] or channelrhodopsin-2[62]. Alternatively, ferritin can be introduced into proliferating (stem) cells using viral vectors, rendering them detectable for MR-imaging[63,64]. Recent progress in this field has also been made by the development of a monoclonal antibody binding to neural precursor cells, coupled to magnetic glyconanoparticles allowing for their detection by MRI[65].While these approaches are quite promising to track eNSCs in individual experimental animals, a major disadvantage of those *in vivo*- labeling approaches is the lack of applicability in human beings due to the invasiveness of the labeling procedure.

Truly non-invasive imaging techniques, utilizing methods that could be translated from the bench to the bedside, are rare. Manganas and colleagues investigated the spectrum of electromagnetic energy from established neurogenic niches using proton magnetic resonance spectroscopy (1H-MRS). They observed a prominent peak in the spectrum at the frequency of 1.28 parts per million (ppm) in the hippocampus of the adult mammalian brain *in vivo*, which was not observed in other regions of the brain[66]. Later studies investigating this phenomenon have shown that it is not specific to eNSCs or neurogenesis, but closely related to apoptosis and quiescence[67,68]. Since apoptosis is a major selection process during neurogenesis, 1H-MRS may be used as an indirect method to detect neurogenesis within the known neurogenic niches and under physiological conditions. Disorders of the CNS associated with increased apoptosis of neural- or other non-neural cells, however, cannot be studied with this approach. Besides, MRS offers quite a low spatial resolution, failing to notice small clusters of cells and leading to the low sensitivity of this method.

We took advantage of the proliferative activity of eNSCs to develop an imaging assay using positron emission tomography (PET). Extensive studies in neurooncology have established the radiotracer 3'-deoxy-3'-[$^{18}$F]fluoro-L-thymidine ([$^{18}$F]FLT) to label proliferating cells in the adult rodent and human brain, allowing for non-invasive imaging of tumor cell proliferation with PET[69-72]. [$^{18}$F]FLT is a thymidine analogue that is incorporated into the DNA of dividing cells-similar to bromodeoxyuridine (BrdU) well established for their immunohistochemical detection- where it is irreversibly trapped, its positron-emitting properties allowing for its non-invasive detection[73]. No evidence of toxicity or other complications have been reported following intravenous injection of [$^{18}$F]FLT[74]. [$^{18}$F]FLT-PET detects ceasing glioma cell proliferation as soon as 3 d after initiation of an anti-proliferative treatment, as we have previously shown in mice and humans[69,72]. Besides tumor cells, proliferating NSCs incorporate [$^{18}$F]FLT both *in vitro* as well as *in vivo* after its systemic (intravenous) injection into adult rats[75]. Thus, [$^{18}$F]FLT labels proliferating eNSCs in the neurogenic niches of the healthy rodent brain with high sensitivity (Figure 2A), corresponding to BrdU-accumulation (Figure 2B). Moreover, [$^{18}$F]FLT-PET quantifies eNSC mobilization mediated by pharmacological stimulation (Figure 2C). The resulting PET-signal can be quantified to reflect the extent of eNSC mobilization[75]. Using a high-resolution PET-scanner and optimizing image reconstruction, the detection level can be as low as ~$10^4$ cells. However, the PET-signal is not specific to endogenous NSC, since other proliferating cells are labeled as well. To increase specificity of this imaging assay, multi-modal imaging protocols can be applied as detailed below.

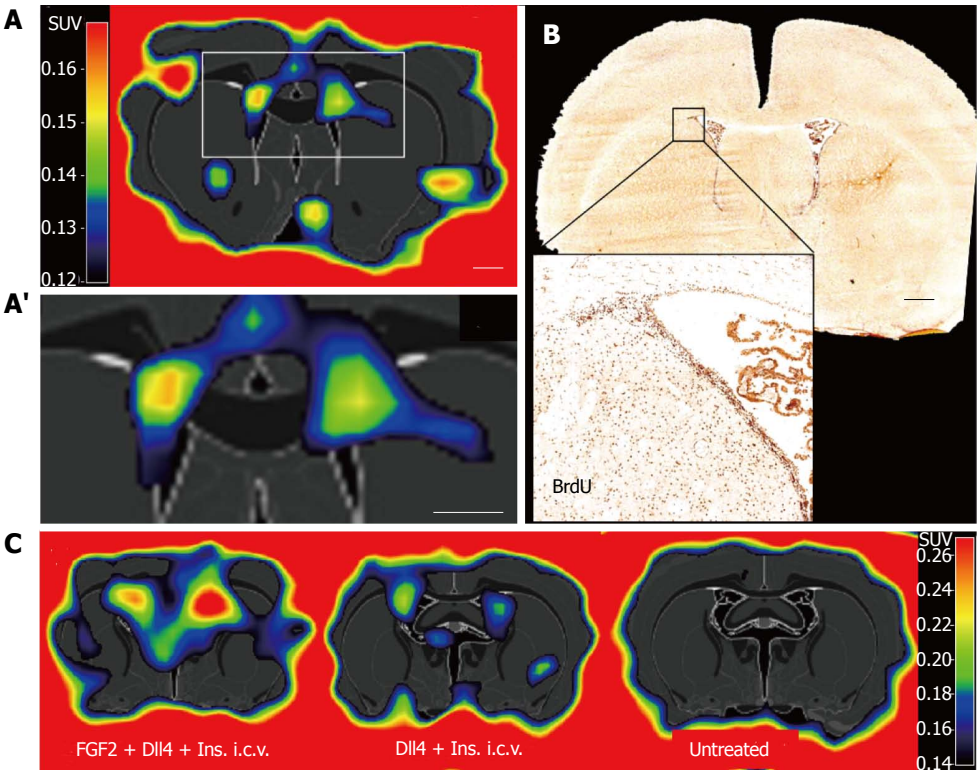


**Figure 2 [$^{18}$F]FLT labels proliferating endogenous neural stem cell in the neurogenic niches of the healthy rodent brain.** A, A': eNSC proliferation in the subventricular zone of adult rats as assessed by [$^{18}$F]FLT-PET; B: The signal corresponds to BrdU-positive cells in the region; C: Activation of eNSC by pharmacological stimulation with fibroblast growth factor 2, delta-like 4, and insulin is visualized with [$^{18}$F]FLT-PET. eNSC: Endogenous neural stem cell; [$^{18}$F]FLT-PET: 3'-deoxy-3'-[$^{18}$F]fluoro-L-thymidine-positron emission tomography; i.c.v.: Intracerebroventricular application. Adapted from Rueger *et al*[75], with permission.

## STEM CELL-MEDIATED REGENERATION AFTER FOCAL CEREBRAL ISCHEMIA

Stroke is the third leading cause of death and the leading cause of adult disability in the Western world[76]. Since rescue of affected neurons can only be achieved by re-perfusion within a very narrow time window, treatment is mainly confined to the amelioration of neurological deficits and the prevention of further events. Especially in the subacute and chronic phase, *i.e.* days to months after stroke, therapeutic options are limited to physiotherapy, ergotherapy and logopedia to rehabilitate impaired neurological functions. However, from the pathophysiological point of view, evolution of ischemic damage is not limited to the minutes after vessel occlusion. After the disruption of blood flow below a threshold has led to rapid necrotic cell death within a localized region, the surrounding tissue that has been spared in this initial phase consecutively also undergoes relevant, but less rapid changes which aim at encapsulating the necrotic tissue, clearing of debris, and facilitating regeneration. These processes - often referred to as neuroinflammation- involve the rapid activation of glial cells (microglia, astrocytes) as well as recruitment of hematogenous cells (granulocytes, T-cells, monocytes/macrophages) from the blood stream[77-82].

While neuroinflammation on the one hand contributes to the evolution of secondary damage to the surrounding tissue by the excessive production of reactive oxygen species and pro-inflammatory cytokines secreted by the immune cells, it also has beneficial effects on the prevention of secondary tissue damage[83]. Besides the containment of necrotic tissue, another most relevant beneficial aspect of stroke-induced neuroinflammation is the induction of a strong regenerative response, leading to a robust expansion of eNSCs[84]. Quality, extent and timing of neuroinflammatory processes determine whether manipulating that particular response after stroke will be deleterious or therapeutically beneficial. The activation of resident microglia can under some circumstances be neurotoxic[85], under others neuroprotective[86], depending on the specific activating conditions[87]. Interestingly, differentially activated microglia also have opposing effects on NSC[88]. eNSC are attracted to the site of the lesion by various inflammation-associated cytokines such as stromal cell-derived factor-1[89-91], tumor necrosis factor-alpha, and interferon-γ[84,92].This mobilization of eNSCs has been shown for various ischemia models in experimental animals, including transient global ischemia[28], transient focal ischemia[26,36], or permanent focal ischemia[93]. However, without any further pharmacological mobilization, the vast majority of newly generated neuroblasts in ischemic stroke models die by the time they have reached the peri-infarct area[36]. Moreover, neurogenesis after stroke seems to play even less a role in humans than it does in rodent models[94]. Those recent findings highlight the

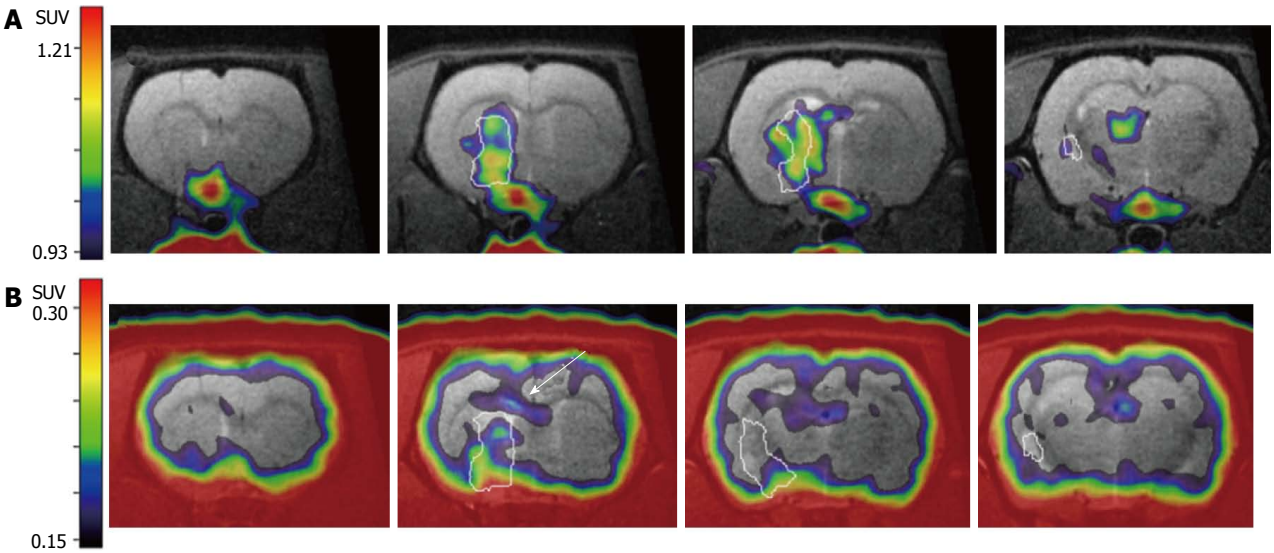


**Figure 3 Conclusive differentiation between cell proliferation from endogenous neural stem cell and immune cells.** After transient focal ischemia (lesion outlined in white), A: Neuroinflammatory processes are visualized with [$^{11}$C]PK11195-PET, depicting inflammation in the infarct core as well as in the ischemic border zone; B: [$^{18}$F]FLT-PET data acquired in the same imaging session without moving the animals in the scanner demonstrates additional cell proliferation in the subventricular zone (white arrow), originating from endogenous neural stem cells. Adapted from Rueger *et al*[97], with permission. [$^{18}$F]FLT-PET: 3'-deoxy-3'-[$^{18}$F]fluoro-L-thymidine-positron emission tomography.

importance of developing novel therapeutic approaches to additionally mobilize and invigorate eNSCs after stroke, either by pharmacological[34,35] or by non-pharmacological treatments[95].

In order to advance those experimental therapeutic approaches into the clinical setting, non-invasive imaging assays have to be established that reliably monitor eNSC activation in the rodent and human brain under the pathophysiological condition of stroke. In this context, the post-ischemic neuroinflammatory processes introduced above resemble a major impediment, since immune cells proliferate in the ischemic brain just as eNSCs do, and [$^{18}$F]FLT-PET does not differentiate between stem cell- and immune cell-derived proliferation. An elegant way to circumvent this problem consists of an imaging assay specific to (neuro-)inflammatory cells that does not visualize eNSCs. The radiotracer [$^{11}$C]PK11195 fulfils this requirement by selectively binding to the translocator protein-18 kDa expressed on inflammatory cells, specifically visualizing post-ischemic cellular neuroinflammatory processes[96]. Since [$^{11}$C]PK11195 is radiolabeled with the isotope 11-C with a half-life of -20 min, sequential PET-imaging with [$^{18}$F]FLT is possible by waiting for -5 half-lives or 100 min between scans. During this time, the animal remains anesthetized within the PET-scanner, avoiding any movement, and enabling an exact co-registration of the imaging data[97]. This co-registered imaging data on [$^{11}$C]PK11195- and [$^{18}$F]FLT-accumulation allows for a conclusive differentiation between cell proliferation from eNSCs and immune cells (Figure 3).

Therefore, PET is a promising tool to image eNSCs in a non-invasive fashion in neurological disorders that can be translated from bench to bedside. However, to further advance the imaging technology in this direction, complementary verification of imaging parameters with immunohistochemical analyses are still needed, and the actual translation of such strategies to a clinical environment has yet a long way to go. However, the non-invasive imaging strategies presented here will help to facilitate translation into the clinical setting, and allow for the exploitation of novel treatment strategies based upon the regenerative potential of eNSCs.

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