How Widespread Are the “Young” Neurons of the Mammalian Brain?

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After the discovery of adult neurogenesis (stem cell-driven production of new neuronal elements), it is conceivable to find young, undifferentiated neurons mixed with mature neurons in the neural networks of the adult mammalian brain. This “canonical” neurogenesis is restricted to small stem cell niches persisting from embryonic germinal layers, yet, the genesis of new neurons has also been reported in various parenchymal brain regions. Whichever the process involved, several populations of “young” neurons can be found at different locations of the brain. Across the years, further complexity emerged: (i) molecules of immaturity can also be expressed by non-dividing cells born during embryogenesis, then maintaining immature features later on; (ii) remarkable interspecies differences exist concerning the types, location, amount of undifferentiated neurons; (iii) re-expression of immaturity can occur in aging (dematuration). These twists are introducing a somewhat different definition of neurogenesis than normally assumed, in which our knowledge of the “young” neurons is less sharp. In this emerging complexity, there is a need for complete mapping of the different “types” of young neurons, considering their role in postnatal development, plasticity, functioning, and interspecies differences. Several important aspects are at stake: the possible role(s) that the young neurons may play in maintaining brain efficiency and in prevention/repair of neurological disorders; nonetheless, the correct translation of results obtained from laboratory rodents. Hence, the open question is: how many types of undifferentiated neurons do exist in the brain, and how widespread are they?

Keywords: adult neurogenesis, brain plasticity, comparative neuroplasticity, immature neurons, doublecortin, subcortical regions

INTRODUCTION

To perform its functions the brain needs stability, in terms of organized (genetically determined) neural networks assuring proper neuronal communication. Neural elements assemble into relatively stable neural circuits after embryonic neurogenesis and early life. Their maturation occurs with remarkable regional differences, leaving spots of immaturity that mostly fade with age, yet, at some locations, continue throughout life. All the exceptions by which definitive stability is not reached (at the synapse, nerve cell/processes, neural network level) do represent plasticity, allowing postnatal structural changes in the system, driven by experience. Even neurogenesis can take place in the adult mammalian brain. It can be viewed as an odd exception to the complex, genetically determined structure of the brain, with its billions of neurons and trillions of synaptic contacts (Chklovskii et al., 2004). The new neurons born in stem cell niches and integrating into pre-existing neural circuits, generated controversies for decades due to a mix of counterintuitive novelty and objective technical difficulties (Kaplan, 2001). Then, a sort of confusion continued...
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Bonfanti and Charvet, 2021). Yet, here come some difficulties, 
linked to a series of facts: (i) neuronal maturation is a multistep 
process consisting of gradients of molecular expression through 
time, sometimes making it nebulous to sharply define stages 
(Kempermann et al., 2004; Sarnat, 2015; (ii) the time period 
corresponding to the phase of immaturity can remarkably vary 
across cell populations and brain regions (La Rosa et al., 2020a); 
(iii) as a consequence, different types of “young” neurons can 
exist and co-exist in different animal ages/brain regions, as 
an expression of different forms of plasticity (Bonfanti and 
Charvet, 2021); (iv) it is becoming more and more evident that 
these aspects can remarkably vary depending on the animal 
species considered, with increasing divergence when comparing 
small-sized, lissencephalic, and large-sized, gyrencephalic brains 
(Kohler et al., 2011; Brus et al., 2013; Paredes et al., 2016a; La Rosa 
et al., 2020b; Franjic et al., 2022; Schmitz et al., 2022).

To give examples, the markers for neuronal immaturity 
doublecortin (DCX) and polysialylated neural cell adhesion 
molecule (PSA-NCAM) were unanimously considered good 
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can be true in neurogenic niches (Brown et al., 2003; but see below), it is not for the so-called “non-newly generated, 
immature” neurons of the cerebral cortex (Gómez-Climent et al., 
2008; Piumatti et al., 2018; Rotheneichner et al., 2018; La Rosa 
et al., 2020a; see below). Recent techniques allowing to go far 
beyond the simple localization of cell markers, such as clonal 
lineage tracing and single-cell transcriptomic profiling, confirm 
the existence of remarkable heterogeneity in cell populations 
and across species (Shohayeb et al., 2021; Franjic et al., 2022; 
Schmitz et al., 2022). Finally, a further kind of re-expression 
of immaturity molecules, in which neurons dedifferentiate to 
a pseudo-immature status (“dematuration”), has been shown to 
occur in aging, inflammation, and hyperexcitation (Hagihara 
et al., 2019). On the whole, the benefit of using markers appears 
more fuzzy than previously thought.

Despite technical and theoretical difficulties, researchers agree 
that the mammalian brain does contain populations of “young” 
neurons, which might be extremely interesting in the perspective 
of a full understanding of brain development/maturation, as 
well as for preventive/therapeutic approaches for neurological 
disorders. It is more and more evident that we cannot mix all 
these cells in the same cauldron; we need to know more about 
their features, origin, location, fate, role in plasticity.

IDENTIFYING THE “YOUNG” NEURONS: 
A TRICKY TASK

Neurodevelopmental studies are accompanied by the use 
of cell markers: molecules that are (or should be) expressed by 
specific populations of cells, indicating their belonging to defined 
categories in the dynamic process of neuronal specification and 
maturity (stem cells, neural progenitors, immature, maturing, 
and mature neurons; Kempermann et al., 2004; Von Bohlen 
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ARE THERE DIFFERENT TYPES OF “YOUNG” NEURONS?

Before the revolution of adult neurogenesis, the classic view 
of the mammalian brain was that of a “non-renewable” tissue, 
in which the only structural changes allowed consisted of 
formation/elimination of synaptic contacts (synaptic plasticity).

In that view, after the end of embryonic neurogenesis, the brain 
was composed of mature neurons having only the possibility 
to change microscopically at the tip of their dendritic/axonal 
processes, or in some cases, to regenerate axonal/dendritic 
portions (Magee and Grienberger, 2020). Adult neurogenesis 
makes it possible the production of new neurons starting from 
novel stem cell “niches” (Doetsch et al., 1999), involving 
processes of cell division, specification, differentiation (in some 
cases migration), maturation, and final integration into the 
pre-existing neural circuits (Kempermann et al., 2004; Aimone 
et al., 2014; Bond et al., 2015; Lim and Alvarez-Buylla, 2016). 
Thousands of studies carried out mostly in rodents have unraveled the molecular and cellular mechanisms of stem cell-
driven neurogenesis in the two main neurogenic sites: the 
ventricular-subventricular zone of the forebrain lateral ventricles 
(V-SVZ; Lim and Alvarez-Buylla, 2016) and the subgranular zone of 
the dentate gyrus in the hippocampus (SGZ; Kempermann 
et al., 2015). Nevertheless, even these “canonical” neurogenic 
processes are characterized by heterogeneity: (i) they are 
abundant and widespread in the whole nervous system of non-
mammalian vertebrates, while highly restricted in mammals 
(Bonfanti, 2011; Lindsey et al., 2018; Lange and Brand, 2020); (ii) 
their extension in the animal lifespan strongly depends on the 
species (Charvet and Finlay, 2018; Snyder, 2019; Bonfanti 
and Charvet, 2021), with dramatic region-specific reduction in
**Figure 1** Summary of the heterogeneity of “young,” undifferentiated neurons existing in the postnatal and adult mammalian brain, on the basis of the current knowledge. (A) Young neurons (e.g., DCX+ cells) can belong to different cell populations, with different origin/fate, likely displaying different types of plasticity: postnatal streams of neuroblasts and postnatal genesis of neuronal populations; adult canonical and non-canonical neurogenic processes. Most of the young neurons can be considered as physiological/homeostatic events, others are reactive neurogenesis to lesion/disease (orange and brown on the right). Two cell populations still undefined (DCX+ neurons in subcortical regions - see Table 1). (Continued)
different regions and animal groups (e.g., the SVZ in humans, Sanai et al., 2011; both neurogenic sites in dolphins; Patzke et al., 2015; Parolisi et al., 2017, 2018); (ii) the maturational times of the newly born neurons can remarkably vary, spanning from 3 to 4 weeks in rodents to 6 months in monkeys (Kohler et al., 2011).

Another source of young neurons is represented by “protracted” neurogenesis: streams of neural blasts or isolated cells generated during late embryogenesis and migrating into the postnatal cortex (Le Magueresse et al., 2011, 2012; Riccio et al., 2012; Paredes et al., 2016b; Bifari et al., 2017; Nascimento et al., 2022). These processes show different origin and features in rodents and primates, likely due to different neurodevelopmental schedules in mammals (Workman et al., 2013; Bonfanti and Charvet, 2021). They seem particularly prominent in human infants, delivering inhibitory interneurons into the frontal and temporal lobes (Paredes et al., 2016b; Nascimento et al., 2022). This delayed addition of neurons can enrich the young neural circuits with new elements while they are highly plastic and modifiable by early life experiences. Similarly, the entire population of cerebellar granule cells is added postnatally, yet, in this case involving multiple rounds of proliferation of progenitor cells forming a transient, subpial germinative layer, then undergoing exhaustion at specific postnatal ages (Altman and Bayer, 1997; Figure 1A).

By using markers typically expressed in newborn neurons, it was suggested that other cell populations located in various “parenchymal” regions (outside the neurogenic stem cell niches) could also be potentially newly generated. In some cases, by using markers of cell division (Ki-67 antigen) and pulse-labeling trace-tracing with tyminide analog (BrdU), the newly born nature of the “young” cells was proven (Dayer et al., 2005; Kokoeva et al., 2005; Luzzati et al., 2006; Ponti et al., 2006, 2008). Yet, substantial differences exist between presumptively neurogenic and canonical neurogenic sites: (i) most of these processes do not start from a morphologically-defined, constitutively-active stem cell niche and/or are not followed by long-term cell survival and functional integration into the pre-existing circuits (so-called “incomplete neurogenesis”; Bonfanti and Peretto, 2011); (ii) some processes are detectable only in some mammalian species, being not present in rodents (Luzzati et al., 2006; Ponti et al., 2006, 2008); (iii) newborn neurons can be found in the brain parenchyma in different experimental conditions, both as lesion-induced, spontaneous “reactive” neurogenesis from the neurogenic sites (Arvidsson et al., 2002) or parenchymal astrocytes (Magnusson et al., 2014; Nato et al., 2015), and after induced lineage reprogramming of glial cells (Mattiagini et al., 2019; Zamboni et al., 2020), including lineage conversion of oligodendrocytes precursors cells (Heinrich et al., 2014) and glia-to-neuron conversion in the hippocampus (Lentini et al., 2021).

In summary, it is more and more evident that different types of young, undifferentiated neurons, stepping away from “canonical” adult neurogenesis, do populate the postnatal and adult brain, possibly contributing to different aspects of its maturation, plasticity, and reaction to lesion/pathology. In this complexity, the simplistic belief that DCX+ cell detection is a proxy for neurogenesis should be replaced by more nuanced landscapes.

### CANONICAL AND NON-CANONICAL NEUROGENESIS: FROM NEURAL STEM CELLS TO “DORMANT” IMMATURE NEURONS

A novel, counterintuitive example of “young” neurons has been introduced by the demonstration that some populations of undifferentiated cells, displaying the same markers of immaturity expressed by newborn neurons, do not divide at all (Gómez-Climent et al., 2008; Piumatti et al., 2018). These cells were firstly described in the piriform cortex layer II (Seki and Arai, 1991; Bonfanti et al., 1992), and are currently (provisionally) referred to as “immature” or “dormant” neurons, since they are generated pre-natally, then remaining in a “standby” state of immaturity for long time (Luzzati et al., 2009; Gómez-Climent et al., 2008; Klempin et al., 2011; Bonfanti and Nacher, 2012; König et al., 2016; Rotheneichner et al., 2018; Benedetti and Couillard-Després, 2022). This idea of “young,” non-dividing neurons has evolved slowly through the years, somehow overwhelmed by the emphasis focused on adult neurogenesis (Bonfanti and Seki, 2021). These neurons can re-activate their maturational process to finally mature and integrate into adult circuits (Rotheneichner et al., 2018; Benedetti et al., 2020). This “neurogenesis without division” can be important for two reasons: first, because they can represent a reservoir of new elements in brain regions that are not endowed with stem/progenitor cells (e.g., the cerebral cortex; Rotheneichner et al., 2018; La Rosa et al., 2019, 2020b; Coviello et al., 2022); second, because it may explain why DCX+ cells can be found in non-neurogenic regions, in the absence of cell division. The molecular mechanisms responsible for the stop/re-start of the maturational process, as well as the role they can play once inserted in the circuits, are currently unexplored (Benedetti and Couillard-Després, 2022). Accordingly, “standby” mode neurons were previously described in the spinal cord...
(Marichal et al., 2009; Kempermann, 2012), thus showing that the puzzling nature of these immature cells can be a general principle in the mammalian nervous system.

For their features, the dormant neurons might be considered as part of the non-canonical neurogenesis, intended as different ways through which the brain can produce/activate new neurons in absence of stem cell division (Bonfanti and Nacher, 2012; Benedetti and Couillard-Després, 2022). The distinction between canonical and non-canonical neurogenesis is at present semantic (Feliciano et al., 2015), since it has been changed/adapted to new discoveries over the years and can evolve in the future, according to the level of heterogeneity of the processes. Non-canonical neurogenesis should include both parenchymal neurogenesis (involving cell division but appearing incomplete) and dormant neurons (not involving cell division after birth but appearing complete). Nevertheless, the final outcome can be the same in

| Brain region | Animal species | Age | Proposed nature | References |
|--------------|----------------|-----|----------------|------------|
| AMYGDALA     | Mouse (Mus musculus) | All ages | No immature cells detectable | [Mostly unpublished negative results and personal observations] Jhaveri et al., 2018 |
|              | Rabbit (Oryctolagus cuniculus) | 3–6 months | Chained of immature neurons (DCX, PSA-NCAM), with a few newly generated elements (BrdU 40 mg/kg) | Luzzati et al., 2003 |
|              | Sheep (Ovis aries) | 1 week | Pre-natally generated (BrdU 20 mg/kg, injected during pregnancy and in adulthood; confocal microscopy) | Piumatti et al., 2018 |
|              | Marmoset (Callithrix jacchus) | 4 years | Newly generated (PSA-NCAM expression) (BrdU 200 mg/kg, light microscopy) | Marlatt et al., 2011 |
|              | Squirrel monkey (Saimiri sciureus) | 3–6 years | Newly generated (PSA-NCAM expression and other markers) (BrdU 50 mg/kg twice a day for 3 days) | Bernier et al., 2002 |
|              | Squirrel monkey (Saimiri sciureus) | 6–12 years | Newly generated (PSA-NCAM expression and other markers) (BrdU 50 mg/kg twice a day for 3 days) | Bernier et al., 2002 |
|              | Macaque (Macaca mulatta) | 1 day–9.5 years | Immature neurons - Cell migration suggested (Bcl-2 expression) (hippocampal lesion) | Chareyron et al., 2021 |
|              | Macaque (Macaca fascicularis, Macaca nemestrina) | 12 years | Immature neurons (DCX and PSA-NCAM expression) | Zhang et al., 2009 |
|              | Macaque (Macaca fascicularis, Macaca nemestrina) | 21 years | Immature neurons (DCX and PSA-NCAM expression) | Fudge et al., 2012 |
|              | Macaque (Macaca fascicularis, Macaca nemestrina) | 31 years | Immature neurons (DCX and PSA-NCAM expression) | Fudge et al., 2012 |
|              | Human (Homo sapiens) | From embryo to adult | Immature neurons until adolescence, then possibly undergoing maturation | Martí-Mengual et al., 2013 |
|              | Human (Homo sapiens) | Immature neurons (expression of PSA-NCAM but not Ki67) | Sorrells et al., 2019 |
|              | Mouse, Rat, Human | 7 weeks (M) | Relation with behavior (DCX expression: protein isolation; RNAseq, qRT-PCR) | Maheu et al., 2021 |
|              | 2–4 months (R) | | | |
|              | 18–65 years (H) | | | |
|              | CLAUSTRUM Sheep (Ovis aries) | 1 week | Pre-natally generated (BrdU 20 mg/kg, injected during pregnancy and in adulthood; confocal microscopy) | Piumatti et al., 2018 |
|              | 4 months | | | |
|              | 2 years | | | |
|              | WHITE MATTER Rabbit (Oryctolagus cuniculus) | 3–6 months | Chained of PSA-NCAM + cells | Luzzati et al., 2003 |
|              | Macaque and Human (Macaca mulatta Homo sapiens) | 2 weeks–12 years (M) | Migrating cells (DCX expression, DCX mRNA) Decreased during infancy | Fung et al., 2011 |
|              | 6 weeks–49 years (H) | Decreased in schizophrenic patients [schizophrenia] | | |
|              | Sheep (Ovis aries) | 1 week | Clusters of immature neurons (non-newly generated in sheep; not coexpressing KitB7 in dolphin) | La Rosa et al., 2018 |
|              | 4 months | | | |
|              | 2 years | | | |
|              | Dolphin (Tursiops truncatus Stenella coeruleoalba) | 1–9 days to adult | | |
canonical adult neurogenesis and dormant neurons, since both processes lead to the addition of new neuronal elements in the neural circuits.

Considering the current knowledge, at least two neuronal populations can be placed into categories on the basis of their origin: the newly generated neurons of the SVZ and SGZ (canonical neurogenesis; extensively studied) and the non-newly generated, cortical “immature” neurons of the cerebral cortex layer II (prenatal origin; far less studied). An ill-defined landscape remains in the inner part of the hemispheres, with reference to populations of subcortical DCX+ neurons of uncertain origin (Figures 1B,B’).

THE CONFUSION STILL EXISTING IN SUBCORTICAL REGIONS

Brain subcortical regions, including gray (amygdala, claustrum) and white matter (external capsule, corpus callosum), are particularly enriched in “young” neurons, with interspecies differences. While a few (or even no) DCX+ neurons can be detected in the amygdala of mice, high amount of these cells has been described in non-human primates (Bernier et al., 2002; Zhang et al., 2009; Mariatt et al., 2011; Fudge et al., 2012; Chareyron et al., 2021) and humans (Martí-Mengual et al., 2013; Sorrells et al., 2019; Table 1). Interestingly, this situation seems to mirror what reported for the cerebral cortex (La Rosa et al., 2020b), thus suggesting that a widespread occurrence of “young” neurons in regions devoid of stem cell niches might be a general trend for non-rodent mammals with reduced canonical neurogenesis (Figures 1B,B’). At present, this is only an hypothesis that should be verified with systematic, quantitative interspecies analyses, similarly to those carried out in the cortex (La Rosa et al., 2020b). Very few is known regarding the real nature/origin of the subcortical DCX+ cells, sometimes interpreted as newly generated in the past (Table 1), when DCX was considered a proxy for neurogenesis (Bonfanti and Seki, 2021). Taking into account that such neurons seem to be important in primates (references in Table 1), the use of experimental approaches aimed at establishing their origin are far from easy. Nonetheless, it is worth mentioning that large populations of dividing glial cells, mostly oligodendrocyte precursors, are widely distributed in the whole brain parenchyma (Clayton and Tesar, 2021; Semënov, 2021), what can represent an important background noise for neurogenesis researchers. Due to the importance of white matter, amygdala and claustrum for proper brain connectivity and functioning, from emotions to conscience, a deeper knowledge of their “young” neurons is needed.

CONCLUSION AND FUTURE PERSPECTIVES

The aim of this Perspective is to underline the extreme heterogeneity of neuroplasticity potentially deriving from different categories of young neurons that populate the mammalian brain with remarkable interspecies variation. The emerging landscape goes beyond the old vision of a “static” brain and also that, more recent, of canonical adult neurogenesis studied in rodents. Prominent postnatal streams of neuroblasts, high amount of “dormant” cortical neurons and unidentified DCX+, immature cells in subcortical regions appear to be a prevalent feature of young-adult gyrencephalic species (Paredes et al., 2016a,b; La Rosa et al., 2020b; Nascimento et al., 2022). The expanded primate brains show multifaceted elements of complexity, involving neuroanatomy, numbers of neurons, and amazing cell type distinctions (Franjc et al., 2022; Schmitz et al., 2022). The different populations of young neurons seem to follow such a complexity: dormant neurons extending in wide regions not endowed with stem cells; postnatal streams delivering inhibitory interneurons; immature neurons becoming principal, pyramidal elements; newborn hippocampal granules being excitatory neurons.

As frequently pointed out, relying exclusively on laboratory rodents comes with several costs that are often not considered, reducing the possibility for proper translation to humans (Brenowitz and Zakon, 2015; Faykoo-Martinez et al., 2017). We need to grasp whether, how, and to which extent, evolution has sculpted interspecies differences from mice to humans, in order to check the current hypothesis: mammals characterized by large brain size, high computational complexity, and long postnatal developmental periods, show lower levels of neurogenesis coexisting with higher content of “young” neurons, and this may represent an evolutionary choice.

By following the ideas presented here, immature/slowly maturing neurons might also persist in neurogenic sites of long-living species, granting the pursuing of plasticity even after stem cell depletion. Even in rodents, protracted development of the newlyborn neurons contributes to long-term plasticity of the hippocampus, after neurogenesis has declined to low levels (Cole et al., 2020). Studies in that sense, conceived out of the traditional box of “stem cell-driven adult neurogenesis” and opened to explore the possible alternative forms of plasticity designed by nature, are urgently needed.

DATA AVAILABILITY STATEMENT

The original contributions presented in this study are included in the article-supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

LB conceived and wrote the manuscript. MG contributed to the research behind the content of the manuscript and to the writing. Both authors contributed to the article and approved the submitted version.
Ghibaudi and Bonfanti

Young Neurons of Mammalian Brain

Rothenreichner, P., Belles, M., Benedetti, B., König, R., Dannehl, D., Kreutzer, C., et al. (2018). Cellular plasticity in the adult murine piriform cortex: continuous maturation of dormant precursors into excitatory neurons. *Cereb. Cortex* 28, 2610–2621. doi: 10.1093/cercor/bhy087

Sanai, N., Nguyen, T., Ihrie, R. A., Mirzadeh, Z., Tsai, H. H., Wong, M., et al. (2011). Corridors of migrating neurons in the human brain and their decline during infancy. *Nature* 478, 382–386. doi: 10.1038/nature10487

Sarnat, H. B. (2015). Immunocytochemical markers of neuronal maturation in human diagnostic neuropathology. *Cell Tissue Res.* 359, 279–294. doi: 10.1007/s00441-014-1988-4

Schmitz, M. T., Sandoval, K., Chen, C. P., Mostajo-Radji, M. A., Seeley, W. W., Nowakowski, T. J., et al. (2022). The development and evolution of inhibitory neurons in primate cerebrum. *Nature* 603, 871–877. doi: 10.1038/s41586-022-04510-w

Seki, T., and Arai, Y. (1991). The persistent expression of a highly polysialylated NCAM in the dentate gyrus of the adult rat. *Neurosci. Res.* 12, 503–513. doi: 10.1016/0168-0102(09)80003-5

Semënov, M. V. (2021). Proliferative capacity of adult mouse brain. *Int. J. Mol. Sci.* 22:3449. doi: 10.3390/ijms22073449

Shohayeb, B., Muzar, Z., and Cooper, H. M. (2021). Conservation of neural progenitor identity and the emergence of neocortical neuronal diversity *Semin. Cell Dev. Biol.* 118, 4–13. doi: 10.1016/j.semcdb.2021.05.024

Snyder, J. S. (2019). Recalibrating the relevance of adult neurogenesis. *Trends Neurosci.* 42, 164–178. doi: 10.1016/j.tins.2018.12.001

Sorrells, S. F., Paredes, M. F., Cebrian-Silla, A., Sandoval, K., Qi, D., Kelley, K. W., et al. (2018). Human hippocampal neurogenesis drops sharply in children to undetectable levels in adults. *Nature* 555, 377–381. doi: 10.1038/nature25975

Sorrells, S. F., Paredes, M. F., Velmeshev, D., Herranz-Pérez, V., Sandoval, K., Mayer, S., et al. (2019). Immature excitatory neurons develop during adolescence in the human amygdala. *Nat. Commun.* 10:2748. doi: 10.1038/s41467-019-10765-1

Sorrells, S. F., Paredes, M. F., Zhang, Z., Kang, G., Pastor-Alonso, O., Biagiotti, S., et al. (2021). Positive controls in adults and children support that very few, if any, new neurons are born in the adult human hippocampus. *J. Neurosci.* 41, 2554–2565. doi: 10.1523/JNEUROSCI.0676-20.2020

Urbán, N. (2022). Could a different view of quiescence help us understand how neurogenesis is regulated? *Front. Neurosci.* 16:878875. doi: 10.3389/fnins.2022.878875

Urbán, N., and Guillemot, F. (2014). Neurogenesis in the embryonic and adult brain: same regulators, different roles. *Front. Cell. Neurosci.* 8:396. doi: 10.3389/fncel.2014.00396

Von Bohlen Und Halbach, O. (2007). Immunohistological markers for staging neurogenesis in the adult hippocampus. *Cell Tissue Res.* 329, 409–420. doi: 10.1007/s00441-007-0432-4

Workman, A. D., Charvet, C. J., Clancy, B., Darlington, R. B., and Finlay, B. L. (2013). Modeling transformations of neurodevelopmental sequences across mammalian species. *J. Neurosci.* 33, 7368–7383. doi: 10.1523/JNEUROSCI.5746-12.2013

Zamboni, M., Llorens-Bobadilla, E., Magnusson, J. P., and Frisén, J. (2020). A widespread neurogenic potential of neocortical astrocytes is induced by injury. *Cell Stem Cell* 27, 605–617.e5. doi: 10.1016/j.stem.2020.07.006

Zhang, X.-M., Cai, Y., Chu, Y., Chen, E.-Y., Feng, J.-C., Luo, X.-G., et al. (2009). Doublecortin-expressing cells persist in the associative cerebral cortex and amygdala in aged nonhuman primates. *Front. Neuroanat.* 3:17. doi: 10.3389/neuro.05.017.2009

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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