ESSAY

Adult Neurogenesis in Humans- Common and Unique Traits in Mammals

Aurélie Ernst¹,², Jonas Frisén¹ *

1 Department of Cell and Molecular Biology, Karolinska Institute, Stockholm, Sweden, 2 Division of Molecular Genetics, German Cancer Research Center (DKFZ), Heidelberg, Germany

* jonas.frisen@ki.se

Abstract

New neurons are continuously generated in specific regions in the adult brain. Studies in rodents have demonstrated that adult-born neurons have specific functional features and mediate neural plasticity. Data on the extent and dynamics of adult neurogenesis in adult humans are starting to emerge, and there are clear similarities and differences compared to other mammals. Why do these differences arise? And what do they mean?

Introduction

For a long time, it was thought that the nervous system is fixed and incapable of regeneration. Although it is indeed true that most neurons in the brain are generated before birth and are never exchanged, it is now well established that new neurons are continuously generated by stem cells in at least two discrete regions in the brain throughout life in most mammals: the hippocampus—a seahorse-shaped structure underneath the cortex that is important for memory formation and cognitive functions; and the olfactory bulb (OB)—a structure located above the nasal cavity that is important for the sense of smell.

At the end of last century, Eriksson, Gage, and colleagues established that new neurons are born in the adult human hippocampus [1]. Only recently, however, has it become possible to acquire quantitative data on the extent and dynamics of adult neurogenesis in humans—by measuring the concentration of the radioactive carbon-14 isotope (¹⁴C) in genomic DNA. Nuclear bomb tests during the Cold War resulted in an enormous increase in atmospheric¹⁴C, which thereafter has declined exponentially, mainly due to uptake by the biotope and diffusion from the atmosphere. The different¹⁴C concentrations in the atmosphere at different times is reflected in the human body, and a cell that was born at a certain time will have a¹⁴C concentration in its genomic DNA corresponding to the time when the cell was born [2]. Measuring¹⁴C in genomic DNA allows retrospective birth dating of cells, and mathematical modeling of such data provides detailed information on the turnover dynamics of a cell population of interest [3]. This research has revealed both that there is more extensive neuronal turnover than many had predicted, and that there is a unique distribution of adult neurogenesis in the adult human brain compared to other mammals. Why is that? And what are the roles of adult neurogenesis in humans?
Adult Hippocampal Neurogenesis Is Conserved Among Mammals

Carbon dating demonstrated that hippocampal neurons are generated at comparable rates in middle-aged humans and mice [4]. However, humans present a somewhat different pattern of adult hippocampal neurogenesis as compared to rodents (Fig. 1). The vast majority of the neurons in the dentate gyrus (DG), the subdivision of the hippocampus with neuronal turnover, is subject to exchange in humans, compared to approximately 10% in mice [4–6]. Moreover, humans show a less pronounced age-dependent decline in hippocampal neurogenesis during adulthood compared to mice [4]. Adult-born hippocampal neurons are more likely to be lost than the neurons born during development in humans [4]. Whether this is also the case in other mammals has not been directly investigated, but data from mice is consistent with this notion [7].

Adult Neurogenesis in the Subventricular Zone and Olfactory Bulb

Neuronal precursor cells, or neuroblasts, are produced not only in the hippocampus but also in the subventricular zone of the LV wall in adult humans, like in other mammals. The density of neuroblasts and the dynamics of its decline with age are very similar between the hippocampus and subventricular zone in humans [8–10]. However, whereas most features of adult hippocampal neurogenesis appear rather highly evolutionarily conserved, there are large differences between humans and other mammals in the output of new neurons from the subventricular zone. In rodents and nonhuman primates, these neuroblasts migrate to the OB (Fig. 1) [11, 12].

Humans appear unique among mammals in that there is negligible, if any, addition of new neurons in the OB after the perinatal period. This conclusion is based on the very few neuroblasts that can be found in the adult human rostral migratory stream, the migratory path from the subventricular zone to the OB, and carbon dating of OB neurons [9, 13]. Although it is not possible to conclude a complete absence of adult OB neurogenesis in adult humans, carbon dating sets the limit to what could go undetected to less than 1% of the OB neurons being exchanged over 100 years [13]. One study reported very large numbers of proliferating cells in the human subventricular zone and rostral migratory stream, implicating substantial adult human OB neurogenesis [14], but only very small numbers of neuroblasts and no evidence of new mature neurons were found in subsequent studies [9, 13, 15].

Adult Striatal Neurogenesis Is Most Pronounced in Humans

The striatum is a forebrain structure underneath the cortex and is involved in regulating motor behaviors and responses to rewarding and aversive stimuli. In rodents, the vast majority of neurons generated in the subventricular zone integrate in the OB. There are, however, studies suggesting the postnatal generation of small numbers of striatal interneurons in mice, rats, and rabbits [16–18]. Adult neurogenesis was also reported in the striatum of untreated and sham-operated adult nonhuman primates [19–21]. In squirrel monkeys, a subset of newborn cells was found to deviate from the rostral migratory stream. Instead of reaching the OB, these cells were shown to migrate into the part of the ventral striatum called the olfactory tubercle, where they displayed a mature neuronal phenotype [20].

In humans, neuroblasts are not restricted to the LV wall, but are also present adjacent to this neurogenic niche, in the striatum (Fig. 1) [22]. Detection of the thymidine analog iodo-deoxyuridine in striatal interneurons, which allows prospective labeling of dividing cells and identification of their progeny, showed the generation of this cell type in adults. Retrospective birth dating of striatal neurons confirmed the postnatal generation of interneurons [22].
It appears likely that the neuroblasts and new neurons in the adult human striatum derive from the neighboring subventricular zone. One major difference in adult neurogenesis between rodents and humans may thus be the direction of neuroblast migration from the subventricular zone, with the OB being the principal destination in most mammals. It is also possible that new
Figure 2. Proportional OB (A), hippocampal (B), and striatal volumes (C). Species are grouped according to major phylogenetic classes varying in phylogenetic distance from humans: nonprimates first (e.g., shrews, tenrecs, hedgehogs), then Strepsirrhine (e.g., lemur), Tarsier, Platyrrhine (e.g., New World monkey), Cercopithecine (e.g., baboon, macaque), Hylobate (e.g., gibbon), Nonhuman hominidae (e.g.,
striatal neurons derive from local cells within the parenchyma [23], perhaps in addition to those from the subventricular zone.

That substantial adult striatal neurogenesis is seen only in humans, and possibly some non-human primates, makes it challenging to study this process in commonly used experimental animals. However, blocking the Notch signaling pathway in astrocytes in the intact striatum of mice triggers neurogenesis in the otherwise intact striatum [23], potentially offering a suitable model to assess the functional role of adult striatal neurogenesis in an experimentally more tractable organism.

Neurogenesis in the Adult Neocortex?
The potential addition of neurons to the adult mammalian neocortex has been a source of controversy. In rodents and nonhuman primates, some reports have suggested that neurogenesis continues in the adult neocortex [16, 24, 25]. Other studies have not detected neurogenesis in this region under physiological conditions [26–28], or have argued for a transient existence of adult-born cortical neurons [29]. In humans, we showed that neocortical neurogenesis is restricted to development [30] and found that cortical neurons are as old as the individual even after stroke [31]. Klempin and colleagues demonstrated that cells expressing the commonly used neuroblast marker doublecortin (DCX) in the mouse piriform cortex (part of the olfactory cortex) were strictly postmitotic [32], and expression of neuroblast markers alone can only be regarded as an indication of potentially ongoing neurogenesis.

Evolutionary Perspectives on Adult Neurogenesis
What could explain the divergent patterns of adult neurogenesis in distinct regions of the mammalian brain? New neurons, as well as changes in the proportion and organization of particular brain structures, offer a selective advantage to individuals by giving them the cognitive adaptability necessary to conquer diverse ecological niches [33]. In general, increasing the size of a brain region enhances the associated functional domains [34]. A decrease in olfactory abilities with evolution is well documented and linked to a reduced dependence on olfaction. This functional regression is associated with a decrease in OB volume across phylogenetic groups, and most extremely in humans (Fig. 2A) [34]. In contrast, relative hippocampal volumes remain rather constant across species, which supports the notion that hippocampal memory seems to be necessary for the success of an organism, regardless of its environmental niche (Fig. 2B) [34]. The neostriatum, comprising the caudate nucleus and the putamen, is a phylogenetically new component of the brain. Over the course of evolution, the striatum enlarged in parallel with the cerebral cortex; it is particularly well developed in higher mammals, including humans (Fig. 2C). This proportional increase of the striatum with evolution implies a heavier reliance on movement coordination, cognition, and emotions.

Indications of the extent of adult neurogenesis in a specific brain region can be inferred from the expression level of markers for immature neurons. In mice, mRNA expression of DCX is much higher in the OB than in the hippocampus and striatum (Fig. 3A). In contrast, in...
Figure 3. Expression levels of the neuroblast marker DCX in the OB, hippocampus, and striatum of adult mice (A) and humans (B) normalized to the expression levels in the non-neurogenic adult cerebellum. In mice, DCX expression is much higher in the OB than in the hippocampus and striatum. In humans, only background levels are detected in the OB, whereas higher DCX expression levels are reached in the human hippocampus and striatum. mRNA expression was measured by in situ hybridization, expression profiling, and RNA sequencing. Data are from geo (GSE 2361, GSE 45878, GSE 46706, GSE 1133, GDS1490, GDS182) and from the Allen Brain Atlas. The data points for the human OB show pooled values for several donors.

doi:10.1371/journal.pbio.1002045.g003
humans, only background levels are detected in the OB. DCX expression levels are comparable in the human hippocampus and in the putamen; they reach the highest values in the caudate nucleus and in the nucleus accumbens (which is part of the ventral striatum) (Fig. 3B). When taking into account additional markers of immature neurons, genes associated with neuronal migration show the highest expression in the striatum in adult humans, as compared to other brain regions (Fig. 4).

These observations are in line with the evolutionary changes in volume and functional performance of the OB, hippocampus, and striatum described above. In the human hippocampus, DCX transcript levels correlate closely with the number of neuroblasts [35], which in turn shows a strong association with the number of newly generated neurons [4]. Estimates of the extent of neurogenesis based on DCX expression support the lack of detectable adult OB neurogenesis in humans [13] and the comparable neuronal turnover rates in the adult human hippocampus and striatum [4, 22].

**Potential Functions for Adult Neurogenesis in Humans**

There is continuous generation of hippocampal neurons throughout life in humans, to an extent comparable to adult neurogenesis in the mouse. Therefore, the level of neurogenesis in the adult human hippocampus may be sufficient to contribute to brain function, and might have similar functions in cognitive adaptability as in rodents [4].
The functional significance of adult striatal neurogenesis remains to be established. Even though the longevity of the adult-born neurons argues for a probable functional integration, it is still to be determined whether the extent of postnatal neurogenesis may be sufficient to be utilized for therapeutic purposes (Box 1). However, low rates of neurogenesis under homeostatic conditions can be increased in response to pathological conditions, and the continuous addition of small numbers of new neurons to the injured striatum over long periods can add up to a significant amount of cells [36]. Furthermore, even a limited number of new neurons can potentially have a substantial functional impact, provided they integrate at critical points in the existing circuitry. Newly generated neurons possess unique properties (e.g., enhanced synaptic plasticity) that allow them to perform special tasks for a limited time after their birth [37, 38].

Which human- or primate-specific striatal functions could necessitate postnatal neurogenesis? The human striatum is now recognized to play a key role for higher cognitive functions, in particular “cognitive flexibility”, the ability to adapt behavioral goals in response to changing contextual demands [39, 40]. Striatal amphetamine-induced dopamine release predicts
individual differences in cognitive flexibility [41]. In children, striatal volume was shown to be associated with neurocognitive performance [42, 43]. Primates possess a number of unique cognitive specializations, some of them being supported by the striatum. In nonhuman primates, the relative striatal volume correlates with the rate of social play behavior across species, suggesting a coevolution of traits [44].

The striatum also has a decisive function in the planning and modulation of movement, which poses the question whether postnatal neurogenesis in the striatum might be required for certain human- or primate-specific motor tasks. In Huntington’s disease, striatal atrophy—which parallels neuronal loss—begins many years before movement abnormalities appear, and the decrease of the striatal volume predicts when motor onset will occur [45].

In addition to the coordination of cognitive and motor functions, the striatum is involved in reward, motivation, and pleasure. In animals, the mesolimbic reward system reinforces biologically vital behaviors, such as eating, sex, or caring for offspring. Over the course of evolution, additional factors became important for successful survival. Humans have the ability to experience pleasure and reinforcing behaviors from more abstract stimuli, such as art or money, which also implicate the mesolimbic striatal area. People differ widely in their willingness to postpone immediate gratification to pursue long-term goals, i.e., how much they discount delayed rewards. Neural activity in the ventral striatum when subjects are asked to think about the future predicts delay discounting [46]. The mesolimbic striatal system also mediates emotion associated with art; specifically, reward value for music can be coded by activity levels in the nucleus accumbens, whose functional connectivity with auditory and frontal areas increases as a function of increasing musical reward [47].

Currently, we can only speculate about the potential functions of adult striatal neurogenesis. Striatal adult neurogenesis may have evolved to provide specific types of neural plasticity in humans and possibly in nonhuman primates. Strategies to modulate postnatal neurogenesis in the striatum of nonhuman primates and evaluate the cognitive, motor, and emotional response might help to uncover what new neurons do in old brains.

References

1. Eriksson PS, Perfilieva E, Bjork-Eriksson T, Alborn AM, Nordborg C, et al. (1998) Neurogenesis in the adult human hippocampus. Nat Med 4: 1313–1317. doi: 10.1038/3305 PMID: 9809557
2. Spalding K, Bhardwaj RD, Buchholz B, Druid H, Frisén J (2005) Retrospective birth dating of cells in humans. Cell 122: 133–143. doi: 10.1016/j.cell.2005.04.028 PMID: 16009139
3. Bergmann O, Bhardwaj RD, Bernard S, Zdunek S, Barnabe-Heider F, et al. (2009) Evidence for cardiomyocyte renewal in humans. Science 324: 98–102. doi: 10.1126/science.1164680 PMID: 19342590
4. Spalding KL, Bergmann O, Alkass K, Bernard S, Salehpour M, et al. (2013) Dynamics of hippocampal neurogenesis in adult humans. Cell 153: 1219–1227. doi: 10.1016/j.cell.2013.05.002 PMID: 23746839
5. Imayoshi I, Sakamoto M, Ohtsuka T, Takao K, Miyakawa T, et al. (2008) Roles of continuous neurogenesis in the structural and functional integrity of the adult forebrain. Nat Neurosci 11: 1153–1161. doi: 10.1038/nn.2185 PMID: 18758458
6. Santos GM, Southon JR, Griffin S, Beaupre SR, Druffel ERM (2007) Ultra small-mass AMS C-14 sample preparation and analyses at KCCAMS/UCI Facility. Nucl Instrum Meth B 259: 293–302. doi: 10.1016/j.nimb.2007.01.172
7. Kempermann G, Gast D, Kronenberg G, Yamaguchi M, Gage FH (2003) Early determination and long-term persistence of adult-generated new neurons in the hippocampus of mice. Development 130: 391–399. doi: 10.1242/dev.00203 PMID: 12466205
8. Gotz C, Frisen J (2012) Neural stem cells and neurogenesis in the adult. Cell Stem Cell 10: 657–659. doi: 10.1016/j.stem.2012.04.005 PMID: 22704503
9. Sanai N, Nguyen T, Ihrle RA, Mirzadeh Z, Tsai HH, et al. (2011) Corridors of migrating neurons in the human brain and their decline during infancy. Nature 478: 382–386. doi: 10.1038/nature10487 PMID: 21964341
10. Knöth R, Singec I, Ditter M, Pantazis G, Capetian P, et al. (2010) Murine features of neurogenesis in the human hippocampus across the lifespan from 0 to 100 years. PLoS One 5: e8809. doi: 10.1371/journal.pone.0008809 PMID: 20126454

11. Lois C, Garcia-Verdugo JM, Alvarez-Buylla A (1996) Chain migration of neuronal precursors. Science 271: 978–981. doi: 10.1126/science.271.5251.978 PMID: 8584933

12. Ming GL, Song H (2011) Adult neurogenesis in the mammalian brain: significant answers and significant questions. Neuron 70: 687–702. doi: 10.1016/j.neuron.2011.05.001 PMID: 21609825

13. Bergmann O, Liebl J, Bernard S, Alkass K, Yeung MS, et al. (2012) The age of olfactory bulb neurons in humans. Neuron 74: 634–639. doi: 10.1016/j.neuron.2012.03.030 PMID: 22632721

14. Curtis MA, Kam M, Nannmark U, Anderson MF, Axell MZ, et al. (2007) Human neuroblasts migrate to the olfactory bulb via a lateral ventricular extension. Science 315: 1243–1249. doi: 10.1126/science.1136281 PMID: 17303719

15. Wang C, Liu F, Liu Y-Y, Zhao C-H, You Y, et al. (2011) Identification and characterization of neuroblasts in the subventricular zone and rostral migratory stream of the adult human brain. Cell Research 21: 1534–1550. doi: 10.1038/cr.2011.83 PMID: 21577236

16. Dayer AG, Cleaver KM, Abouantoun T, Cameron HA (2005) New GABAergic interneurons in the adult neocortex and striatum are generated from different precursors. J Cell Biol 168: 415–427. doi: 10.1083/jcb.200407053 PMID: 15684031

17. Luzzati F, De Marchis S, Fasolo A, Peretto P (2006) Neurogenesis in the caudate nucleus of the adult rabbit. J Neurosci 26: 609–621. doi: 10.1523/JNEUROSCI.4371-05.2006 PMID: 16407559

18. Inta D, Alfonso J, von Engelhardt J, Kreuzberg MM, Meyer AH, et al. (2008) Neurogenesis and widespread forebrain migration of distinct GABAergic neurons from the postnatal subventricular zone. Proc Natl Acad Sci U S A 105: 20994–20999. doi: 10.1073/pnas.0807059105 PMID: 19095802

19. Bedard A, Coissette M, Levesque M, Parent A (2002) Proliferating cells can differentiate into neurons in the striatum of normal adult monkey. Neurosci Lett 328: 213–216. doi: 10.1016/S0304-3940(02)00530-X PMID: 12147309

20. Bedard A, Levesque M, Bernard PJ, Parent A (2002) The rostral migratory stream in adult squirrel monkeys: contribution of new neurons to the olfactory tubercle and involvement of the antiapoptotic protein Bcl-2. Eur J Neurosci 16: 1917–1924. doi: 10.1046/j.1460-9586.2002.02263.x PMID: 12453055

21. Tonchev AB, Yamashima T, Sawamoto K, Okano H (2005) Enhanced proliferation of progenitor cells in the subventricular zone and limited neuronal production in the striatum and neocortex of adult macaque monkeys after global cerebral ischemia. J Neurosci Res 81: 776–788. doi: 10.1002/jnr.20604 PMID: 16047371

22. Ernst A, Alkass K, Bernard S, Salehpour M, Perl S, et al. (2014) Neurogenesis in the striatum of the adult human brain. Cell 156: 1072–1083. doi: 10.1016/j.cell.2014.01.044 PMID: 24561062

23. Magnusson JP, Goritz C, Tatarishvili J, Dias DO, Smith EM, et al. (2014) A latent neurogenic program in astrocytes regulated by Notch signaling in the mouse. Science 346: 237–241. doi: 10.1126/science.346.6206.237 PMID: 25301628

24. Gould E, Reeves AJ, Graziano MS, Gross CG (1999) Neurogenesis in the neocortex of adult primates. Science 286: 548–552. doi: 10.1126/science.286.5439.548 PMID: 10521353

25. Bernard PJ, Bedard A, Vinet J, Levesque M, Parent A (2002) Newly generated neurons in the amygdala and adjoining cortex of adult primates. Proc Natl Acad Sci U S A 99: 11464–11469. doi: 10.1073/pnas.172403999 PMID: 12177450

26. Komack DR, Rakic P (2001) Cell proliferation without neurogenesis in adult primate neocortex. Science 294: 2127–2130. doi: 10.1126/science.1065467 PMID: 11739948

27. Ehninger D, Kempermann G (2003) Regional effects of wheel running and environmental enrichment on cell genesis and microglia proliferation in the adult murine neocortex. Cereb Cortex 13: 845–851. doi: 10.1093/cercor/13.8.845 PMID: 12853371

28. Koketsu D, Mikami A, Miyamoto Y, Hisatsune T (2003) Nonrenewal of neurons in the cerebral neocortex of adult macaque monkeys. J Neurosci 23: 937–942. PMID: 12574422

29. Gould E, Vail N, Wagers M, Gross CG (2001) Adult-generated hippocampal and neocortical neurons in macaques have a transient existence. Proc Natl Acad Sci U S A 98: 10910–10917. doi: 10.1073/pnas.18154698 PMID: 11526209

30. Bhardwaj RD, Curtis MA, Spalding KL, Buchholz BA, Fink D, et al. (2006) Neocortical neurogenesis in humans is restricted to development. Proc Natl Acad Sci U S A 103: 12564–12568. doi: 10.1073/pnas.0605177103 PMID: 16901981

31. Huttner HB, Bergmann O, Salehpour M, Racz A, Tatarishvili J, et al. (2014) The age and genomic integrity of neurons after cortical stroke in humans. Nat Neurosci 17: 801–803. doi: 10.1038/nn.3706 PMID: 24747576
32. Klempin F, Kronenberg G, Cheung G, Kettenmann H, Kempermann G (2011) Properties of doublecortin-(DCX)-expressing cells in the piriform cortex compared to the neurogenic dentate gyrus of adult mice. PLoS One 6: e25760. doi: 10.1371/journal.pone.0025760 PMID: 22022443

33. Kempermann G (2012) New neurons for ‘survival of the fittest’. Nat Rev Neurosci 13: 727–736. PMID: 22948073

34. Koscik TR, Tranel D (2012) Brain evolution and human neuropsychology: the inferential brain hypothesis. J Int Neuropsychol Soc 18: 394–401. doi: 10.1017/S1355617712000264 PMID: 22948073

35. Kang HJ, Kawasawa YI, Cheng F, Zhu Y, Xu X, et al. (2011) Spatio-temporal transcriptome of the human brain. Nature 478: 483–489. doi: 10.1038/nature10523 PMID: 22301440

36. Thored P, Arvidsson A, Cacci E, Ahlenius H, Kallur T, et al. (2006) Persistent production of neurons from adult brain stem cells during recovery after stroke. Stem Cells 2005-0281 PMID: 16210404

37. Ge S, Yang CH, Hsu KS, Ming GL, Song H (2007) A critical period for enhanced synaptic plasticity in newly generated neurons of the adult brain. Neuron 54: 559–566. doi: 10.1016/j.neuron.2007.05.002 PMID: 17521569

38. Schmidt-Hieber C, Jonas P, Bischofberger J (2004) Enhanced synaptic plasticity in newly generated granule cells of the adult hippocampus. Nature 429: 184–187. doi: 10.1038/nature02553 PMID: 15107864

39. Cools R, Clark L, Robbins TW (2004) Differential responses in human striatum and prefrontal cortex to changes in object and rule relevance. J Neurosci 24: 1129–1135. doi: 10.1523/JNEUROSCI.4312-03.2004 PMID: 14762131

40. Cools RI, Ivry RB, D’Esposito M (2006) The Human Striatum is Necessary for Responding to Changes in Stimulus Relevance. The Journal of Cognitive Neuroscience 18: 1973–1983. doi:10.1162/jocn.2006.18.12.1973 PMID: 17129181

41. Samanez-Larkin GR, Buckholtz JW, Cowan RL, Woodward ND, Li R, et al. (2013) A thalamocorticos-triatal dopamine network for psychostimulant-enhanced human cognitive flexibility. Biol Psychiatry 74: 99–105. doi:10.1016/j.biopsych.2012.10.032 PMID: 23273721

42. Fryer SL, Mattson SN, Jernigan TL, Archibald SL, Jones KL, et al. (2012) Caudate volume predicts neu-rocognitive performance in youth with heavy prenatal alcohol exposure. Alcohol Clin Exp Res 36: 1932–1941. doi: 10.1111/j.1530-0277.2012.01811.x PMID: 22551091

43. Chaddock LE K. I. Shaurya Prakash R., VanPatter M., Voss M. W., Pontifex M. B., Raine L. B., Hillman C. H., Kramer A. F. (2010) Basal Ganglia Volume Is Associated with Aerobic Fitness in Preadolescent Children. Developmental Neuroscience 32: 249–256. doi: 10.1159/000316648 PMID: 20693803

44. Lewis Graham K (2011) Coevolutionary Relationship Between Striatum Size and Social Play in Nonhu-man Primates. American Journal of Primatology 73: 314–322. doi: 10.1002/ajp.20898 PMID: 21328590

45. Aylward EH, Liu D, Nopoulos PC, Ross CA, Pierson RK, et al. (2012) Striatal volume contributes to the prediction of onset of Huntington disease in incident cases. Biol Psychiatry 71: 822–828. doi: 10.1016/j.biopsych.2011.07.030 PMID: 21907324

46. Cooper NK J. W. Kyu Kim B., Zauberman G. (2013) Brain Activity in Valuation Regions while Thinking about the Future Predicts Individual Discount Rates. The Journal of Neuroscience 33: 13150–13156. doi: 10.1523/JNEUROSCI.0400-13.2013 PMID: 23926268

47. Zatorre RJ, Salimpoor VN (2013) From perception to pleasure: music and its neural substrates. Proc Natl Acad Sci U S A 110 Suppl 2: 10430–10437. doi: 10.1073/pnas.1301228110 PMID: 23754373

48. Wei B, Nie Y, Li X, Wang C, Ma T, et al. (2011) Emx1-expressing neural stem cells in the subventricular zone give rise to new interneurons in the ischemic injured striatum. Eur J Neurosci 33: 819–830. doi: 10.1111/j.1460-9568.2010.07570.x PMID: 21219481

49. Arvidsson A, Collin T, Kirik D, Kokaia Z, Lindvall O (2002) Neuronal replacement from endogenous pre-cursors in the adult brain after stroke. Nat Med 8: 963–970. doi: 10.1038/nm747 PMID: 12161747
53. Macas J, Nern C, Plate KH, Momma S (2006) Increased generation of neuronal progenitors after ischemic injury in the aged adult human forebrain. J Neurosci 26: 13114–13119. doi: 10.1523/JNEUROSCI.4667-06.2006 PMID: 17167100

54. Marti-Fabregas J, Romaguera-Ros M, Gomez-Pinedo U, Martinez-Ramirez S, Jimenez-Xarrie E, et al. (2010) Proliferation in the human ipsilateral subventricular zone after ischemic stroke. Neurology 74: 357–365. doi: 10.1212/WNL.0b013e3181ccc3c00 PMID: 20054008

55. Curtis MA, Penney EB, Pearson AG, van Roon-Mom WM, Butterworth NJ, et al. (2003) Increased cell proliferation and neurogenesis in the adult human Huntington’s disease brain. Proc Natl Acad Sci U S A 100: 9023–9027. doi: 10.1073/pnas.1532244100 PMID: 12853570

56. Curtis MA, Penney EB, Pearson J, Dragunow M, Connor B, et al. (2005) The distribution of progenitor cells in the subependymal layer of the lateral ventricle in the normal and Huntington’s disease human brain. Neuroscience 132: 777–788. doi: 10.1016/j.neuroscience.2004.12.051 PMID: 15837138

57. Camp AJ, Wijesinghe R (2009) Calretinin: modulator of neuronal excitability. Int J Biochem Cell Biol 41: 2118–2121. doi: 10.1016/j.biocel.2009.05.007 PMID: 19450707

58. Mitchell IJ, Cooper AJ, Griffiths MR (1999) The selective vulnerability of striatopallidal neurons. Prog Neurobiol 59: 691–719. doi: 10.1016/S0301-0082(99)00019-2 PMID: 10845758