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NSR 3676 1–11

ARTICLE IN PRESS

Neuroscience Research xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Neuroscience Research

journal homepage: www.elsevier.com/locate/neures

Review article

Mechanisms of brain evolution: Regulation of neural progenitor cell diversity and cell cycle length

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ARTICLE INFO

Article history:
Available online xxx

Keywords:
Brain evolution
Cell cycle
Neural progenitor cells
Cortical architecture
Gyrification
Cell fate determination

ABSTRACT

In the last few years, several studies have revisited long-held assumptions in the field of brain development and evolution providing us with a fundamentally new vision on the mechanisms controlling its size and shape, hence function. Among these studies, some described hitherto unforeseeable subtypes of neural progenitors while others reinterpreted long-known observations about their cell cycle in alternative new ways. Most remarkably, this knowledge combined has allowed the generation of mammalian model organisms in which brain size and folding has been selectively increased giving us the means to understand the mechanisms underlying the evolution of the most complex and sophisticated organ. Here we review the key findings made in this area and make a few conjectures about their evolutionary meaning including the likelihood of Martians conquering our planet.

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1. Diversity in brain size, shape and function

One of the most remarkable features of the forebrain, and particularly the cerebral cortex, is its extraordinary phenotypic diversity, namely referred to size and shape. Quite outstandingly, the variety of brain sizes among vertebrates spans five orders of magnitude, from 80 mg in the green lizard to 7.8 kg in the sperm whale (http://faculty.washington.edu/chudler/facts.html). Brain shapes are also found in a remarkably varied *repertoire* (Fig. 1). In reptiles, e.g. snakes, the olfactory bulb is very long and massive compared to the rest of the telencephalon, including a small and smooth cortex. In birds the cortex is also smooth and the olfactory bulb is notably small, whereas the basal telencephalon is by far the largest part of the brain. Finally, in the mammalian brain, the cerebral cortex represents the largest part, and itself displays a wide variety of shapes from spheroidal (manatee, human) to spindle-shaped (rabbit, giant ant-eater) (Fig. 1) (Welker, 1990). Because in general terms the cerebral cortex is a sheet of neural tissue, this may be deformed in the three-dimensional space forming folds and fissures (Welker, 1990). In fact, folding turns out to be a very effective strategy to fit a very large cerebral cortex sheet (with a very large surface area) inside a reduced volume, thus limiting overall head size. As a general rule, big brains (e.g. human) are usually highly folded, or gyrencephalic, whereas small brains (e.g. mouse) are usually completely smooth, or lissencephalic. Finally, if we look at the cytoarchitectural organization of the cerebral cortex this diversity becomes further increased. For example, the murine cerebral cortex is organized in 6 layers but layers 2 and 3 are usually considered together, while in primates not only layers

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http://dx.doi.org/10.1016/j.neures.2014.04.004

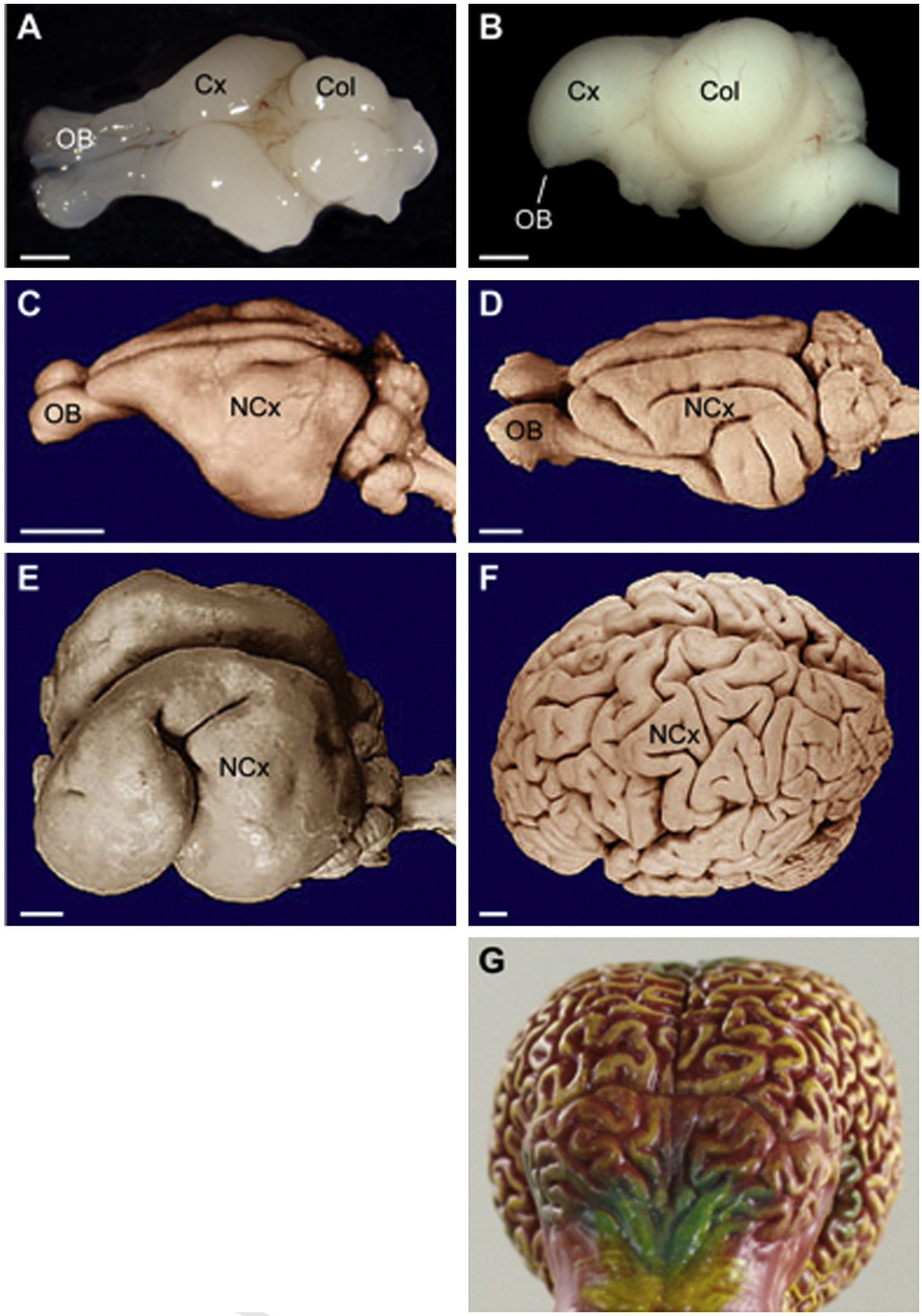

Fig. 1. Diversity of brain phenotypes across phylogeny. External views of the brain of different vertebrates demonstrating morphological diversity. (A) Red cornsnake (*Pantherophis guttatus*); (B) Japanese quail (*Coturnix coturnix japonica*); (C) Jack rabbit (*Lepus americanus*); (D) Giant ant-eater (*Myrmecophaga tridactyla*); (E) Manatee (*Trichecus manatus latirostris*); (F) Human (*Homo sapiens sapiens*); (G) Martian. Col, colliculus; Cx, cortex; NCx, neocortex; OB, olfactory bulb. Scale bars: *A*, 1 mm; *B*, 2 mm; *C–F*, 1 cm.

Source: Photographs are from Chen et al. (2012) (B), www.brainmuseum.org (C–F), and http://derekwinnert.com (G).

2 and 3 are clearly distinguishable, but in striate visual cortex we can distinguish layers 2/3A, 3B, 4A, 4B, 4Cα and 4Cβ (Callaway, 1998). In some anecdotic cases we even find greater variety, like in the giraffe where layer 2 is organized in discontinuous clusters of neurons separated by cell-sparse regions (Defelipe, 2011).

In addition to size, shape and cytoarchitecture, phenotypic diversity of the cerebral cortex extends into its most important feature: function. It is generally assumed, and even accepted, that cerebral cortex size and the degree of cortical folding are equivalent, if not directly proportional, to the degree of intelligence. But evidently this is an extremely anthropocentric view of brain diversity, fundamentally based on the belief that humans are the most intelligent creatures on Earth and that our brain is functionally unmatched. But how do we measure intelligence? Whereas the human capacity for changing the world is undoubtedly superior to any other species, how much of this can be attributed to our brain performance and how much to our opposable thumbs or any other peculiar human feature (Roth and Dicke, 2005)? That is, are we truly much smarter than dolphins or just more capable of building and handling tools? If elephants and whales have bigger brains

Please cite this article in press as: Borrell, V., Calegari, F., Mechanisms of brain evolution: Regulation of neural progenitor cell diversity and cell cycle length. Neurosci. Res. (2014), http://dx.doi.org/10.1016/j.neures.2014.04.004