NEUROSCIENCE

Evolution of the human brain

A human-specific gene is a determinant of the cognitive architecture of the human cerebral cortex

By **Colette Dehay**[1] *and* **Henry Kennedy**[1,2]

Since early hominids emerged 5 million years ago, humans have evolved sizable brains to support higher cognitive functions. In particular, the human cerebral cortex is greatly expanded, allowing accommodation of the evolutionary increases in the number of cortical areas, the functional modules that subserve perception, attention, motor control, cognition, memory, and learning. Duplicated genes specific to the *Homo* lineage have played key roles in human speciation, particularly in the development of the highly complex human brain (*1*) and the circuits of the cerebral cortex (*2*). On page 546 of this issue, Heide *et al.* (*3*) identify *ARHGAP11B* [Rho guanosine triphosphatase (GTPase) activating protein 11B], a human-specific duplicated gene, as a regulator of human cerebral cortex development. By expressing *ARHGAP11B* in marmosets, a smooth-brained primate, this study explores the influence of the gene on expansion of the primate cortex.

The human neocortex is marked by an important increase in surface area and its radial dimension, the latter due to the selective enlargement of the supragranular layers (*4*). Supragranular neurons have an important role in the integration of ascending and descending cortico-cortical pathways that underlie information transfer and processing between the numerous hierarchically organized cortical areas in primates. Therefore, the specific expansion of supragranular neurons contributes to the cognitive functions of primates, culminating in humans (*4*). Much of the origin of this expansion can be attributed to primate-specific features of corticogenesis, including an expanded progenitor pool in the developing primate cerebral cortex: the outer subventricular zone (OSVZ) (*5*), which includes specialized progenitors called basal radial glial cells (bRGs) (*6*). bRGs are endowed with extensive proliferative capacities and generate mostly supragranular neurons (*7*).

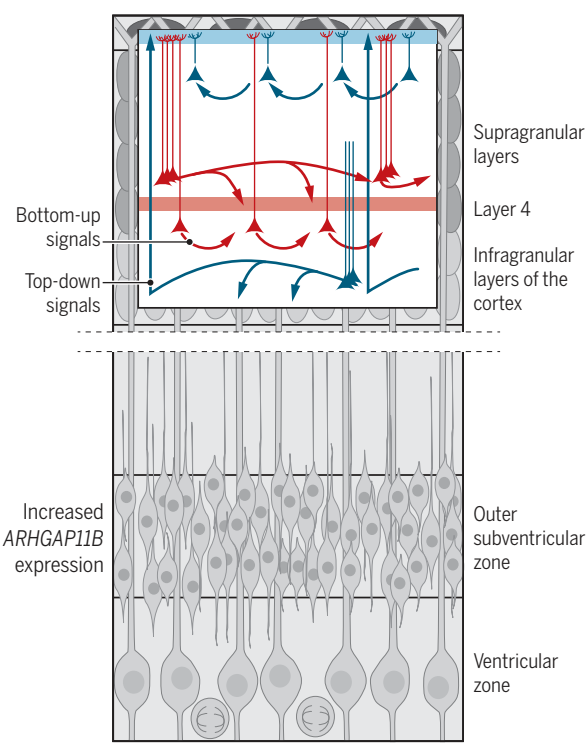
ARHGAP11B has received much attention because it is specifically enriched in cortical bRGs (*8*). When locally overexpressed in mouse or ferret cortex, *ARHGAP11B* boosts bRG proliferation and increases the numbers of cortical neurons (*8*, *9*). These observations suggest that this gene could link specific aspects of primate corticogenesis and characteristic features of the adult primate cortex architecture. To test this, Heide *et al.* expressed *ARHGAP11B* in the developing cortex of the embryonic marmoset. When *ARHGAP11B* is expressed under the control of the human promoter and upstream regulatory sequences, the transgenic mid-gestation marmoset exhibits an enlarged developing cortex with signs of folding. The crucial observation is that there is a selective increase in the numbers of neurons in the supragranular layers. This "humanization" of the marmoset fetal cortex demonstrates that expression of *ARHGAP11B* in bRGs in a primate substrate has the capacity to contribute to neocortical expansion and supragranular complexification during human evolution. *ARHGAP11B*-induced expansion of the cortical progenitor pool is mediated by metabolic changes in mitochondria, particularly increased glutaminolysis, a characteristic of highly mitotically active cells (*10*). This illustrates how cell metabolism—one of the most ancient of biological networks—participates in shaping the human lineage.

How does the increased rate of supragranular neuron production, resulting from *ARHGAP11B* expression in OSVZ progenitors, affect the functional architecture of the cortex? And do these effects provide evolutionary insights? In the cortical hierarchy, areas are linked by a dense network of ascending (or bottom-up) and descending (or top-down) pathways forming a highly distributed hierarchy (*11*). Current theories of hierarchical processing of information in the cortex, including predictive coding theory, postulate that top-down messages signaling expectations interact in the supragranular layers with bottom-up activity from the sensory periphery, thereby enabling the brain to actively infer the causes of sensory stimulus (*12*). Recent structural analysis reveals that in the supragranular layers, top-down and bottom-up connections form two opposing streams, thereby constituting a counterstream architecture (*11*) (see the figure).

During evolution, there is a marked increase in the numbers of cortical areas, so that larger numbers of human supragranular

Shaping the human cortex

Heide *et al.* show that *ARHGAP11B* [Rho guanosine triphosphatase (GTPase) activating protein 11B] boosts proliferation in the outer subventricular zone, leading to increased production of cells destined for the supragranular layers. The counterstream architecture of the supragranular layers comprises feedback projections carrying top-down signals (blue arrows) that interact with feedforward projections (red arrows) carrying bottom-up sensory signals. The integration of these two pathways into the local microcircuit is a key feature of hierarchical processing in the primate cortex and will be favored by increased numbers of supragranular neurons.



GRAPHIC: MELISSA THOMAS BAUM/*SCIENCE*

[1]University of Lyon, Université Claude Bernard Lyon 1, Inserm, Stem Cell and Brain Research Institute U1208, 69500 Bron, France. [2]Institute of Neuroscience, State Key Laboratory of Neuroscience, Chinese Academy of Sciences Key Laboratory of Primate Neurobiology, Shanghai 200031, China. Email: colette.dehay@inserm.fr; henry.kennedy@inserm.fr

neurons are required to integrate cortico-cortical circuits compared to non-human primates. In addition, because of the specific coding properties of the supragranular layers, increases in the number of supragranular neurons are expected to increase the circuit efficiency of these layers (*13*), which, along with their complexification (*14*), could drive gains in computational power and the capacity to integrate top-down and bottom-up signals. The architecture of the primate brain has therefore evolved for the computational mechanisms that affect human perception and sense of self; this also has implications for the evolution of memory and learning.

The findings of Heide *et al*. illuminate how a molecular mechanism driving cortical development can scale up phylogenetically ancestral primate brains to the complexity of the human brain. ARHGAP11B-mediated humanization of the marmoset fetal cortex demonstrates the involvement of a human-specific duplicated gene in the expansion of the supragranular layers. The effect of *ARHGAP11B* expression on OSVZ progenitors and their cortical progeny reinforces the importance of recent findings showing that human-specific regulatory elements are enriched in the OSVZ and the adult supragranular layers (*15*). Together with the role of *SRGAP2* (Slit-Robo-GTPase activating protein 2), a human-specific duplicated gene that acts on cortical neuron complexity and synaptic circuitry (*2*), these findings point to crucial evolutionary adaptations converging on the cardinal structural features of the human cortex that underlie its unrivaled computational and cognitive performance. Future studies will need to address the effect of *ARHGAP11B* expression at different time points in corticogenesis, its potential role in determining human specific cell types in the brain, and its intersection with the etiology of neurological disorders (*4*, *14*, *15*). ■

REFERENCES AND NOTES

1. M. Y. Dennis, E. E. Eichler, *Curr. Opin. Genet. Dev.* **41**, 44 (2016).
2. C. Charrier *et al.*, *Cell* **149**, 923 (2012).
3. M. Heide *et al.*, *Science* **369**, 546 (2020).
4. A. M. M. Sousa, K. A. Meyer, G. Santpere, F. O. Gulden, N. Sestan, *Cell* **170**, 226 (2017).
5. I. H. Smart, C. Dehay, P. Giroud, M. Berland, H. Kennedy, *Cereb. Cortex* **12**, 37 (2002).
6. D. V. Hansen, J. H. Lui, P. R. Parker, A. R. Kriegstein, *Nature* **464**, 554 (2010).
7. M. Betizeau *et al.*, *Neuron* **80**, 442 (2013).
8. M. Florio *et al.*, *Science* **347**, 1465 (2015).
9. N. Kalebic *et al.*, *eLife* **7**, e41241 (2018).
10. T. Namba *et al.*, *Neuron* **105**, 867 (2020).
11. J. Vezoli *et al.*, bioRxiv 2020.04.08.032706 (2020).
12. R. P. Rao, D. H. Ballard, *Nat. Neurosci.* **2**, 79 (1999).
13. K. D. Harris, T. D. Mrsic-Flogel, *Nature* **503**, 51 (2013).
14. J. Berg *et al.*, bioRxiv 2020.03.31.018820 (2020).
15. H. Won, J. Huang, C. K. Opland, C. L. Hartl, D. H. Geschwind, *Nat. Commun.* **10**, 2396 (2019).

10.1126/science.abd1840

STRUCTURAL BIOLOGY

Fine-tuning receptor–G protein activation and signaling

The activation rate of downstream G proteins imprints receptor signaling

By **Guillaume Lebon**

G protein–coupled receptors (GPCRs) are eukaryotic plasma membrane receptors that are organized into four classes in humans: A, B, C, and Frizzled. They internalize extracellular stimuli by activating a common pool of intracellular signaling partners such as the heterotrimeric G proteins (composed of Gα, β, and γ subunits) that subsequently induce an appropriate cellular response. Recent advances in cryo–electron microscopy (cryo-EM) enables challenging structures of GPCR signaling complexes to be solved, providing unprecedented insights about the molecular basis of their signal transduction (*1*). Qiao *et al*. (*2*) reported two cryo-EM structures of the class B human glucagon receptor (GCGR) G_s and G_i complexes, which helped clarify GCGR G protein selectivity. On page 523 of this issue, Hilger *et al*. (*3*) report a cryo-EM structure of a GCGR-G_s complex and reveal the effect of conformational changes on GCGR signaling properties. These studies support a common mechanism for class B receptor activation.

Activation of G proteins by GPCRs trigger nucleotide exchange and hydrolysis occurring in sequential transition of conformational states from inactive guanosine disphosphate (GDP)-bound forms, to the intermediate nucleotide-free state, then to the active guanosine triphosphate (GTP)–bound G proteins that activate downstream signaling. Accordingly, GPCRs function as guanine nucleotide exchange factors (GEFs). GCGR physiology and signaling are challenging our knowledge of GPCR activation mechanisms. For example, circulating glucagon generated by pancreatic α-cells activates the GCGR and controls glucose homeostasis in the liver (*4*). Once glucagon activates the GCGR-G_s signaling complex in hepatocytes, the G_s protein interacts with adenylate cyclase, which in turn induces production of the second messenger cyclic adenosine monophosphate (cAMP). GCGR has a specific functional signature when considering the amplitude and time scale of glucagon-induced cAMP production compared with other hormones such as epinephrine, which activates the class A GPCR β2-adrenergic receptor (β2AR). It is also common that a GPCR interacts with several G proteins—such as G_s, G_i, and G_q—and GCGR is no exception: It can also activate G_q and G_i proteins (*5*).

But how do GPCRs achieve the functional selectivity to activate specific G proteins? The two cryo-EM structures of GCGR-G_s and GCGR-G_i complexes solved by Qiao *et al*. reveal the large movement of the intracellular tip of transmembrane helix 6 (TM6), which is tilted outward, to accommodate the α5 helix from both G_s and G_i. TM6 movement is a molecular signature of class A and B GPCR active conformations. GCGR TM5 and TM7 undergo a similar motion, but to a lesser extent. This creates a large cavity for the G protein to bind. Conformational changes leading to GCGR activation occur in a different manner than for class A receptors. The conserved residues of the PXXG motif in TM6 are repositioned, and TM6 locally unwinds, which results in a sharp kink that tilts the straight intracellular tip of TM6 away from the receptor core (*2*, *3*). Such a kink was reported for several class B GPCRs (*6*), and the superposition of the corresponding receptor signaling complexes clearly illustrates this conserved feature compared with class A receptors, for which there is no kink; instead, TM6 simply bends over, with some degree of variability, depending on the receptor (*1*).

The G protein–binding site of type B GPCRs compares well with class A GPCRs coupled to G_s, although it is larger and accommodates a carboxyl-terminal (C-terminal) extremity of the α5 helix from both G_s and G_i (see the figure). There are substantial differences in the sequences of G_s and G_i α5 helices, which is indicative of the requirement of a larger binding site for G_s. The overall contact surface resulting from G_s and G_i subunit engagement with GCGR also differs. This molecular interface is mainly mediated by the α5 helix C-terminal extremity and is larger for G_s, 802 Å^2, compared with 551 Å^2 for G_i.

Another difference is the contribution of the receptor intracellular loop 2 (ICL2) in

Institut de Génomique Fonctionnelle (IGF), University of Montpellier, CNRS, INSERM, Montpellier, France. Email: guillaume.lebon@igf.cnrs.fr

Evolution of the human brain

Colette Dehay and Henry Kennedy

Science **369** (6503), 506-507.
DOI: 10.1126/science.abd1840