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Response to Comment on "Universality in the Evolution of Orientation Columns in the Visual Cortex"

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Meng *et al*. conjecture that pinwheel density scales with body and brain size. Our data, spanning a 40-fold range of body sizes in Laurasiatheria and Euarchonta, do not support this conclusion. The noncolumnar layout in Glires also appears size-insensitive. Thus, body and brain size may be understood as a constraint on the evolution of visual cortical circuitry, but not as a determining factor.

We presented a comparative study of visual cortical orientation columns and pinwheels in three mammalian species whose evolutionary paths separated more than 65 million years ago (*1*). For this purpose, we introduced methods to measure pinwheel density objectively— i.e., insensitive of image data preprocessing [(*1*) and supporting online material (SOM) of (*1*), pp. 3–12 and 29–41]. We found that statistical measures characterizing the spatial layout of pinwheels from the scale of individual hypercolumns to the entire primary visual cortex (V1) were virtually identical, agreeing with an accuracy of a few percent. To understand how distinct evolutionary lineages can independently evolve this common design, we examined a broad set of mathematical models for the developmental self-organization of orientation columns [(*1*) and SOM of (*1*), pp. 13–62]. We found that models from a symmetry-defined class, exhibiting a universal (i.e., model-independent) solution set, robustly predict every aspect of the common design when suppressive long-range interactions are dominant [(*1*) and SOM of (*1*), pp. 13–41)]. This suggests that developmental network self-organization has canalized the evolution of neuronal circuitry underlying orientation maps in these species into the common design. A predicted signature of this mechanism is a pinwheel density close to the mathematical constant π. Confirming this prediction, we found that mean pinwheel density was indeed statistically indistinguishable from π (±2%).

Meng *et al*. claim that pinwheel density is not an invariant but a function of V1 size (*2*). They conjecture a pinwheel density scaling law that can be approximated by

$$\rho = 3/2\log_{10}(A/3\ \text{mm}^2)$$

where A is V1 surface area [figure 1 in (*2*)]. Their scaling law predicts substantial differences between ferrets/tupaias, galagos, and cats. With 80 mm^2, 200 mm^2, and 450 mm^2 V1 size, respectively (*3*, *4*), pinwheel density in cats (galagos) should be 53% (28%) larger than in ferrets/tupaias. Our methods to accurately estimate pinwheel density are well suited to test this prediction. Figure 1A presents measured pinwheel densities for the four species graphed against body weight. Pinwheel densities appear invariant with respect to body weight. The hypothesis that mean pinwheel density in cat (galago) is more than 50% (20%) larger than in ferrets can be rejected with virtual certainty [$P < 0.0001(0.0001)$, bootstrap test]. Meng *et al*. suggest greater variation in pinwheel density across species; however, those data were derived from studies with small sample sizes using first-generation optical imaging methods that are subject to various systematic errors described in detail in [SOM of (*1*), figures S2 and S3 and pp. 3–12]. Our analysis unambiguously indicates that pinwheel density is a genuine invariant feature of orientation column layout over a wide range of V1 sizes and that it is insensitive to hypercolumn size (Fig. 1, B and C).

Figure 1D presents V1 design type for Laurasiatheria, Euarchonta, and Glires varying in body weight over 5 orders of magnitude. As this display suggests, the interspersed, "salt-and-pepper" layout observed in rodent and lagomorph (Glires) V1 (*3*, *5*) provides no evidence for a size-dependent V1 design. Interspersed layouts constitute a qualitatively distinct design type [for further discussion, see (*1*), p. 1115] from that observed in Laurasiatheria and Euarchonta. Glires exhibit this layout for V1 sizes that vary from 3 to 80 mm^2, irrespective of ecological niche and visual behavior (*3*). Indeed, Glires cortex generally deviates in cellular composition from primate or carnivore cortex (*6*, *7*) and exhibits interspersed organization also for direction selectivity in primary somatosensory cortex and characteristic frequency in primary auditory cortex (*8*, *9*). Thus, the interspersed layout is a putative Glires-typical trait.

However, the functional organization of V1 must not be imagined to be completely independent of area size. Orientation hypercolumns have a spatial extend on the order of a millimeter, with hypercolumn areas ranging between 0.4 mm^2 and 1.4 mm^2. For species in which V1 size approaches this range, it becomes hard to conceive of V1 as being organized by a system of orientation columns. A size constraint prohibiting a conventional system of orientation columns should, for instance, apply to the V1 of etruscan shrews (*Suncus etruscus*), which is confined to a mere 0.2 mm^2 of visual cortex (*10*). It also appears plausible for the last common ancestor of carnivores and primates, called the boreoeutherian ancestor [SOM of (*1*), pp. 63–64]. Its closest living relative, the tenrec (*Echinops telfairi*), weighs about 100 g and has a visual cortex that totals 2 mm^2 (*11*). Fossils of stem eutherians [*Asioryctes nemegetensis*, 43 g, 0.5ml endocranial volume (EV); *Kennalestes gobiensis*, 39 g, 0.3ml EV; *Zalambdalestes lechei*, 83 g, 1ml EV] indicate even smaller body and brain sizes (*11*, *12*) (Fig. 1E). If the boreoeutherian ancestor in fact lacked a system of orientation columns due to such a size constraint, then larger visual cortices exhibiting orientation columns must have independently emerged in the evolutionary lineages leading to extant primates, tree shrews, and carnivores. In any event, as indicated in Fig. 1E, visual cortical organization has been challenged—among other changes—by a dramatic increase of animal and, consequently, V1 size in the wake of the Cretaceous-Tertiary (K-T) extinction event 65 million years ago [for further discussion, see the SOM of (*1*), pp. 63–64]. In view of these aspects, it seems remarkable that lineages separated over the entire evolutionary history of boreoeutherian mammals precisely follow a common design.

In summary, studying animals of different V1 size confirmed pinwheel density as a genuine invariant of orientation map design. The interspersed organization found in Glires constitutes a distinct design type also insensitive to V1 size. Orientation columns so far have only been found in large visual areas and may not exist in very

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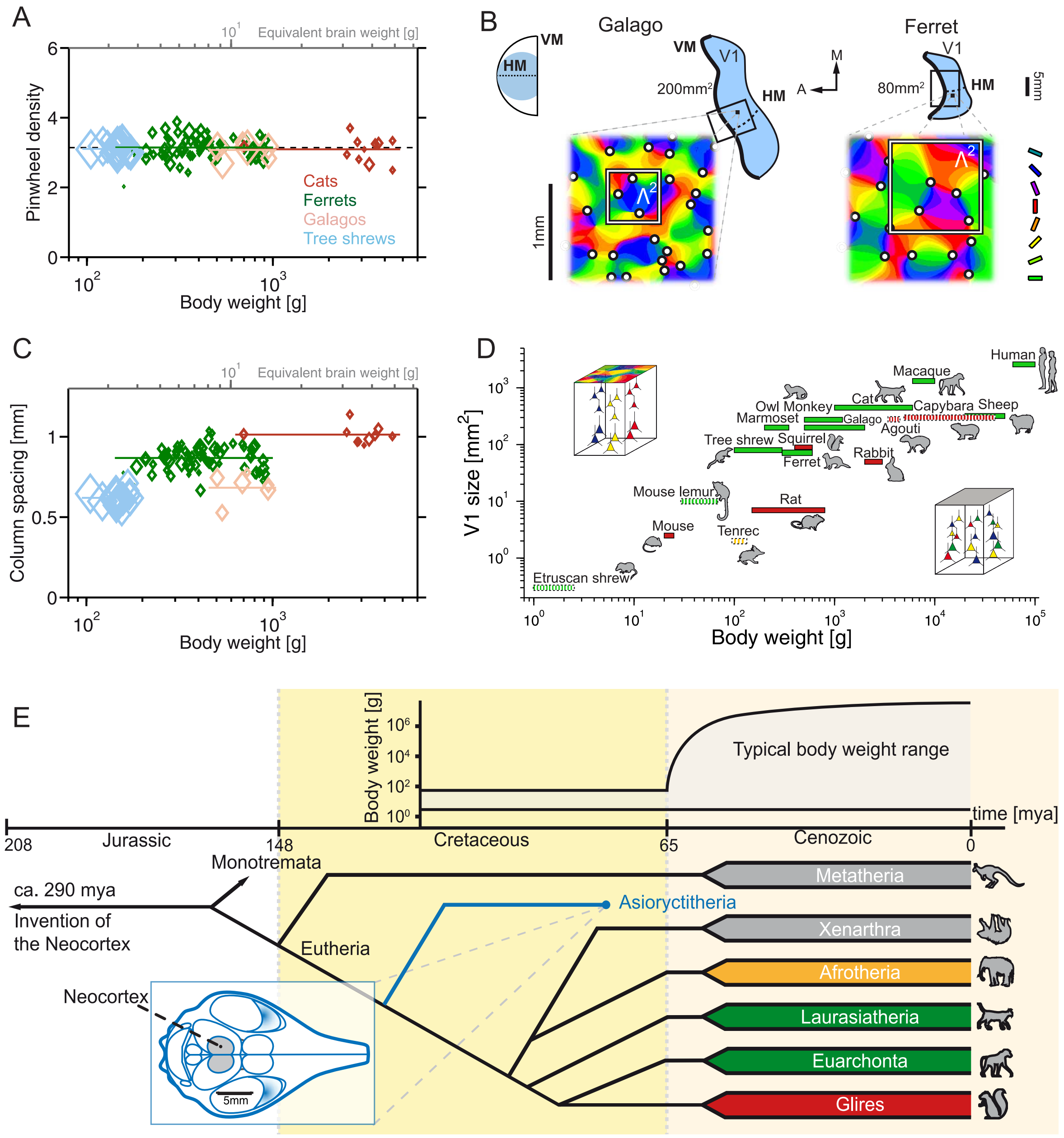

Fig. 1. Brain size, V1 surface area, and pinwheel density in the evolution of visual cortical organization. (**A**) Pinwheel density is size invariant. Dimensionless pinwheel densities ρ versus body size m_{body} in tree shrew, galago, ferret, and cat. Tree shrew, $\rho = 3.11$ (3.05, 3.16), mean and 95% confidence interval (CI), $n = 20$ hemispheres (hem.); galago, $\rho = 3.07$ (2.87, 3.23), $n = 6$ hem.; ferret, $\rho = 3.15$ (3.07, 3.22), $n = 70$ hem.; cat, $\rho = 3.09$ (2.89, 3.29), $n = 11$ hem.; symbol size proportional to size of the measured region in units of one hypercolumn Λ^2. Solid lines indicate average pinwheel density in each species. Black dashed line is at $\rho = \pi$. Linear regression $\rho = \rho_0 + \rho_1 \log_{10}(m_{\text{body}}/\text{g})$ estimates a slope $\rho_1 = -0.02$ (-0.14, 0.11), not significantly different from zero. Top axis indicates equivalent brain weight (*13*). (**B**) Galago and ferret differ strongly in surface area and hypercolumn size but have indistinguishable pinwheel density. (Top) V1 surface area and representation of the visual hemifield in galago (left) and ferret (right). Blue area, V1; HM, horizontal meridian; VM, vertical meridian. (Bottom) Typical orientation map insets in galago (left) and ferret (right); black box identifies typical imaging field in experiments. White dots, pinwheels; white square, area of one hypercolumn. Galago V1 contains more than 400 orientation hypercolumns, ferret V1 only about 100. (**C**) Orientation column spacings versus body weights. Orientation column spacing exhibits substantial interspecies differences. Solid lines indicate average column spacing in each species. Tree shrew, $\Lambda = 0.62$ mm (0.61, 0.63), $n = 20$ hem.; galago, $\Lambda = 0.68$ mm (0.62, 0.74), $n = 6$ hem.; ferret, $\Lambda = 0.87$ mm (0.85, 0.88), $n = 70$ hem.; cat, $\Lambda = 1.01$ mm (0.99, 1.04), $n = 11$ hem.; symbol size as in (A). (**D**) Both columnar and interspersed arrangements of orientation preference appear over wide and overlapping ranges of V1 surface area and body weight. The two design types are indicated by schemes: upper scheme, columnar; lower scheme, interspersed. Green color indicates species of the Laurasiatheria or Euarchonta clade. Red color indicates Glires species. Filled/hatched bars indicate known/unknown spatial organization of orientation preference. Green filled bars indicate columnar, red filled bars indicate interspersed organization. [Data from (*3*, *4*, *10*, *14*, *15*)] (**E**) Mesozoic and cenozoic macroevolution of extant mammals showing divergence into six major clades: Monotremes, Marsupials, Afrotheria, Xenarthra, Laurasiatheria, and Euarchontoglires, which split into Euarchonta and Glires (*11*). Eutherian size expansion after the K-T extinction event is indicated on top. Large V1 architecture independently evolved at least six times during the radiation of extant mammals. The anatomical scheme depicts the cranium of a representative late cretaceous stem eutherian (Asioryctitherian). This close relative to the last common ancestor of extant Eutheria had a small V1, presumably lacking orientation columns [SOM of (*1*), pp. 63–64).

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small brains such as those of many late cretaceous mammals. In their descendants, the K-T extinction event enabled an explosive increase in body and brain size millions of years after the major mammalian lineages had separated. It triggered the separate evolution of architectures for large visual areas in distinct lineages. Our theory of universality in network self-organization explains how they could independently develop a common design. It is the only known explanation for the quantitatively precise agreement of orientation column layouts in tree shrew, galago, ferret, and cat. Other mammalian lineages are predicted to adopt the same design when using qualitatively similar developmental mechanisms. Precise quantification of visual cortical architecture in mammals from the extremes of body and brain sizes in all therian clades will help to clarify this fascinating chapter of brain evolution with rigor and certainty.

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