



Punctuated evolution of visual cortical circuits? Evidence from the large rodent *Dasyprocta leporina*, and the tiny primate *Microcebus murinus*

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Abstract

Recent reports of the lack of periodic orientation columns in a very large rodent species, the red-rumped agouti, and the existence of incompressible hypercolumns in the lineage of primates, as demonstrated in one of the smallest primates, the mouse lemur, strengthen the interpretation that salt-and-pepper and columns-and-pinwheel mosaics are two distinct functional layouts. These layouts do neither depend on lifestyle nor scale with body size, brain size, absolute neuron numbers, binocular overlap, or visual acuity, but are primarily distinguishable by phylogenetic traits. The predictive value of other biological signatures such as V1 neuronal surface density and the central-peripheral density ratio of retinal ganglion cells are reconsidered, and experiments elucidating the intracortical connectivity in rodents are proposed.

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Introduction

Sensory systems adapt themselves to environmental statistics allowing for optimal representation and

extraction of sensory features [1]. Localized oriented band-pass receptive fields emerge when two global objectives are given for image analysis, namely, representing the information sparsely and preserving the statistical dependencies [2]. In agreement, the majority of vertebrate visual systems, mammals (e.g. Ref. [3]) and their early placental ancestors [4], marsupials [5], but also fishes [6], birds [7], and reptiles [8] produced this kind of receptive fields.

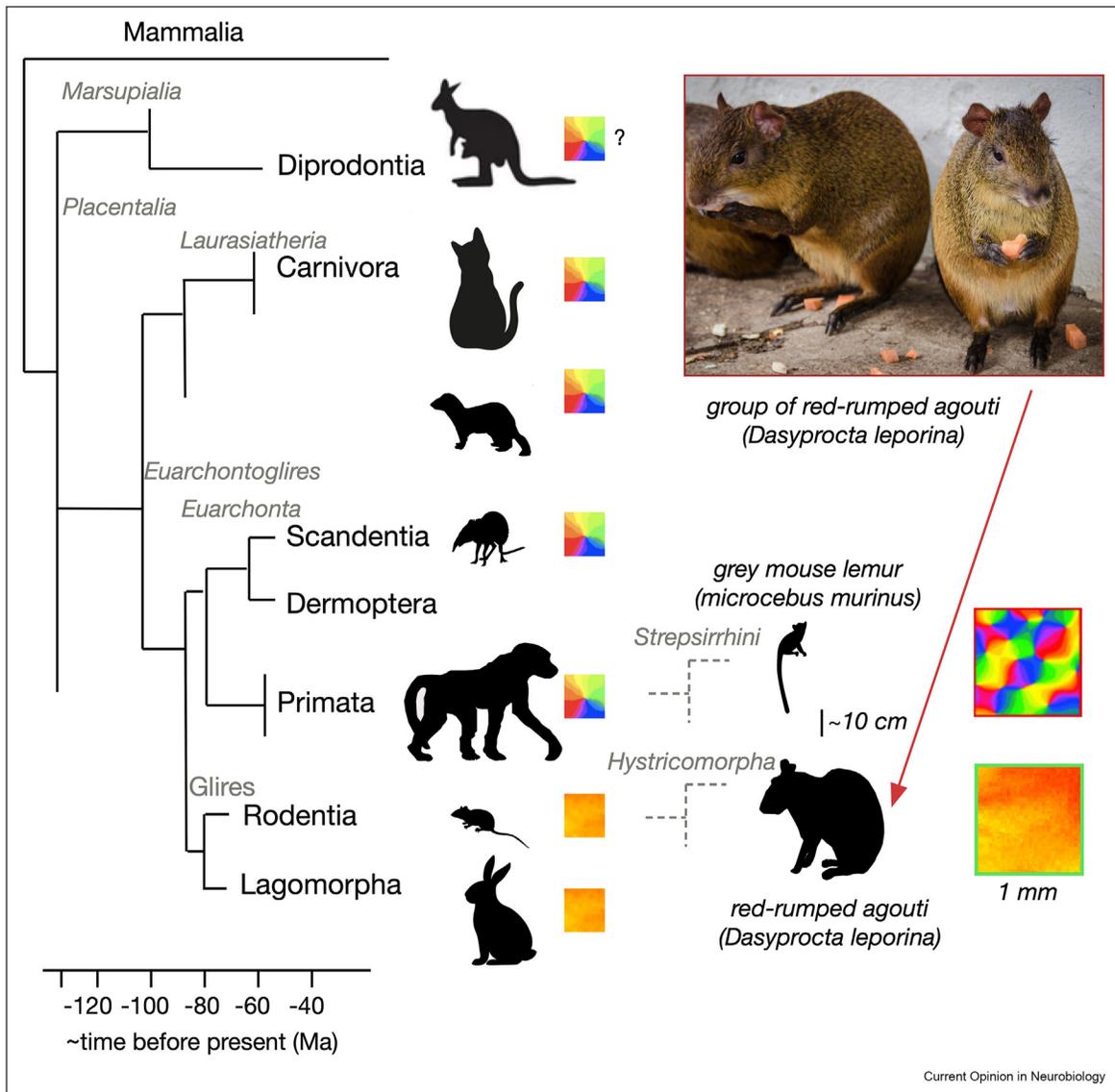
Thereby, primates and their ancestral relatives [9], Scandentia [10], and carnivores [11,12] arrange their contour-selective neurons for all possible orientations in periodically repeating vertical hypercolumns [13] of species- and area-characteristic width [14]. Orientation preference in a hypercolumn circles smoothly singularities of the representation, which were termed pinwheel centers [15] in which each of the orientations is equally detected [16]. Pinwheel-like mosaics appear when rainbow color-coding the pixels of the obtained recordings according to the interpolated orientation of those contours, which evoked the best responses. These maps have been observed in all visual Euarchontan mammals, including the smallest primate, the mouse lemur *Microcebus murinus* [17] but not in rodents or lagomorphs (Figure 1).

Rodents lack periodic orientation columns but cluster similarly tuned neurons locally

Although rodents and rabbits possess orientation-selective neurons (mouse [18], grey squirrel [19] grasshopper mouse [20], rabbit [21], agouti [22]), they do not express the typical periodic layout but a salt-and-pepper like arrangement of orientation-selective neurons, also termed interspersed (rat [16], grey squirrel [19], rabbit [23]), ordered only by retinotopy [24]. More recent reports from mice claim that neurons distribute not entirely randomly but express similar preferences within vertical clusters [25]. Those match mini-columns of roughly 30 μm in diameter, which are supposedly the smallest vertical unit of a canonical cortical microcircuit in vertebrate brains [26] but can also be seen as packing artifacts from radial scaffolding during development [27].

The agouti (Figure 2) caught our attention because it is a diurnal and highly visual rodent and has the

Figure 1



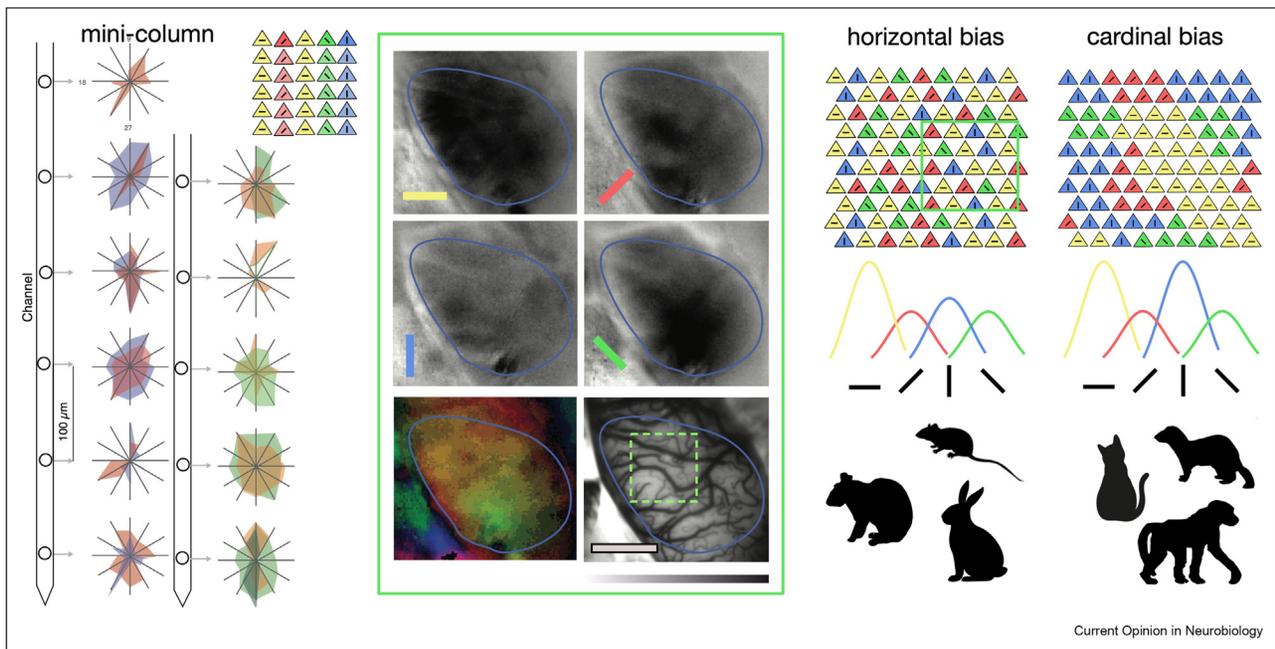
Orientation maps are present in small primates but not in large rodents. Periodic columnar maps of orientation-selective neurons in the primary visual cortex arranged in pinwheel-like mosaics have been observed in all primates, carnivores, and Scandentia investigated. In contrast, rodents and lagomorphs present a salt-and-pepper or interspersed layout, although they supposedly split from the Euarchonta sister group after the Laurasiatheria (tree drawn after [60]). New data from the largest visual, diurnal rodent investigated so far, the red-rumped agouti (*Dasyprocta leporina*) and one of the world's smallest primates, the grey mouse lemur (*Microcebus murinus*), confirm that the emergence of patterned maps does not depend on a limit body or cortex size. Upper right: a group of agoutis feeding bi-manually, courtesy of M.F. de Oliveira. Lower right: Real size comparison between mouse lemur and agouti and their respective orientation layouts in 1 mm² cortex. Mouse lemurs have pinwheel mosaics with larger hypercolumn width than expected from their cortex size. Maps reprinted from Refs. [17,22] with permission from Elsevier. Agouti orientation map inset from the green-framed area in Figure 2. Abbreviation: Ma, million years. Colors: clade, subclade, and order in grey; species in black.

largest primary visual cortex (320 mm², Garcia et al., personal communication) investigated in the rodent order so far. Furthermore, it exhibits small receptive fields (6,2 + 3.7deg) throughout its visual streak representation and an orientation, direction, and spatial frequency selectivity only slightly lower than that of cats [22]. This puts agoutis into the bigger picture within the discussion of the factors driving visual cortical map

formation. The recent report confirms the general lack of periodic maps and pinwheel centers but a local clustering (in-depth) of neurons preferring similar contour orientations emphasizing that this cortical layout is rodent-specific.

This poses the obvious question of whether the circuits constructing cortical orientation selectivity are different

Figure 2



Agoutis present clustering of similar orientation preferences in depth, and a bias for horizontal orientation preference, but no periodic maps. Left: Polar tuning curves of sorted single-unit spiking activity obtained from in-depth recordings at intervals of 100 μm orthogonal to the cortical surface. Different colors denote units isolated from the same recording site. Middle: Unfiltered activity maps obtained with intrinsic signal imaging from agouti V1 during visual stimulation with a grating of different orientations (color bars). Horizontal orientation evokes the strongest activation, both in a single unit and hemodynamic activity ([22], their Figs. 6 and 8), and there are no obvious orientation columns discernible. Lower left: Color-coded polar map, right vessel image. Scale bar: 1 mm. Green inset: position of the polar maps depicted in Figure 1. Figure rearranged from Ref. [22] with permission from Elsevier. Right: Horizontal orientation biases are present in many animals with a visual streak (mice [64], agouti [22], rabbit [66]); cardinal biases are found dominantly in frontal-eyed mammals (e.g. monkey [84], cat [85], ferret [12]).

in rodents. There seems to be more orientation and direction-selective neurons in the rodent geniculate nucleus [28–30] than in the cats (for review [31]). Therefore, the heritage of cortical selectivity from orientation and direction selective-neurons in the LGN (and retina) of rodents have been strongly discussed [28–30]. However, by now, this mechanism has been largely discarded as the major source of orientation selectivity in the primary visual cortex (for review [32]). Rather, it was confirmed that oriented simple receptive fields in V1 — as in the cat — could be constructed by the convergence of spatially separated thalamic afferents from overlapping ON and OFF regions [33], thereby linearly amplifying the thalamocortical input [34].

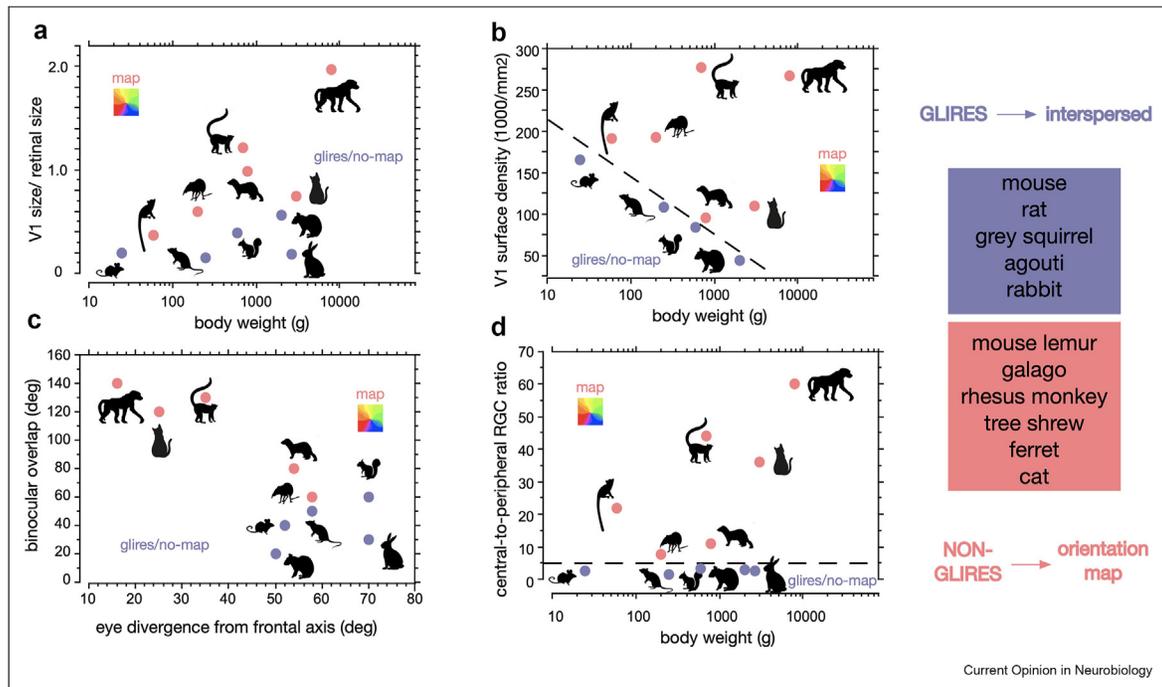
Which factors could be excluded to contribute to the functional layout of orientation maps?

Several theoretical models included single biological parameters or their ratio to explain why preferences for visual features are mapped in a crystalline manner onto the cortical surface in primates and carnivores but not in rodents. At least three of them cited agouti as a ‘missing

link’, predicting either an interspersed layout because they are lateral-eyed rodents with a visual streak [35] with small rodent-type astrocytic arbors delimiting the width of the hypercolumn [36], or orientation maps with pinwheel-like mosaics because of their V1 size [37], neuron number [38] and/or their retinal-cortical mapping ratio [39]. On the basis of the new data, it can be concluded that the three latter factors, i.e. V1 size, neuron number, and the retino-cortical mapping ratio, are not predictive of the layout (Figure 3).

Early on, it was suggested that modular maps exist in order to minimize neuronal wiring length with maximum coverage [13,40–42] and reduce the cortical volume needed for local operations [43]. Thus, neurons with similar preferences would be selectively connected and located in close vicinity to each other to save wiring costs. Indeed, neurons in different hypercolumns but with similar properties also tend to be selectively interconnected and along trajectories that are correlated with their orientation (for review [44]). When assuming a dynamical formation of orientation maps [45,46], especially those excitatory long-range interactions pose constraints such that short pathways with fast signal

Figure 3



Phylogenetic traits, biological parameters, and their predictive value for the functional layout of orientation preference revisited. All members of the order Glires investigated do not establish periodic orientation preference maps (blue colors), in contrast to primates and carnivores (red colors), and one can predict the emergence of a periodic orientation map based on the phylogeny. a: A previous model aimed to predict map layout solely on the ratio between V1 size and retina. The new data speak in favor of refuting this hypothesis (values taken from Ref. [39], agouti retina [51], agouti V1, M. Garcia, personal communication, mouse lemur [17]). b: Rodents increased their cortex size in relation to body and brain size with a different power function than primates, leading to relatively lower cell densities. Thus the ratio of V1 neuronal surface density and body size is a good predictor of which layout is adopted. Values are taken from Refs. [38,52,53]. c: Glires consistently exhibit lateral eyes and small binocular overlap, tree shrew and ferret, which have periodic maps, cannot be easily separated from that group. Values from Ref. [35]; agouti: own data. d: Ibbotson and Jung [35] suggested the ratio between the central and peripheral RGC (retinal ganglion cell) density as a parameter separating species with salt-and-pepper and periodic orientation maps. The new data points from mouse lemur (value from Ref. [17]) and agouti [22] fit well into this idea. Other values are taken from Ref. [35].

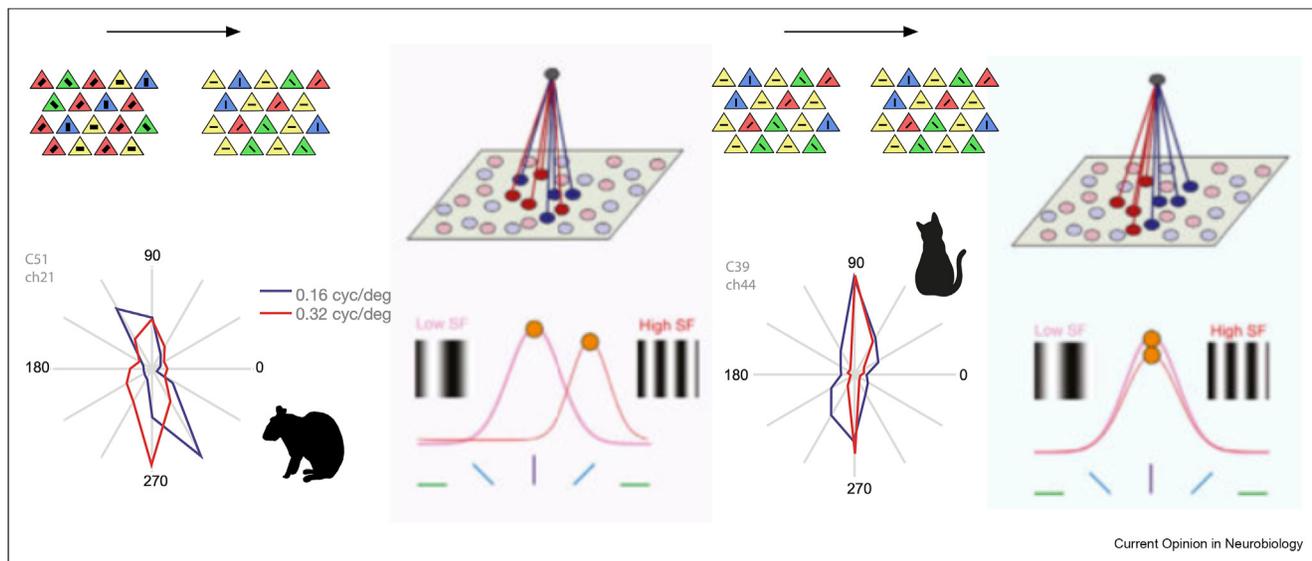
transmission and small-world properties might be only achieved through a periodic arrangement of orientation-selective domains (for review [47]), especially relevant when brains get bigger [37] and when neuron numbers increase [38].

However, the new results from agouti with a rodent V1 of 320 mm^2 (calculated from [48], and own data) and mouse lemur with a primate V1 of 48 mm^2 [17] emphasize that the design adopted to represent orientation selectivity is size-invariant. Specifically, columns are not as miniaturized as expected from the mouse lemur's brain size, indicating that reducing the neuronal size and increasing packing density poses a natural limit to this kind of architecture because a minimum number of neurons is needed for local operations. Indeed, the number of neurons per orientation hypercolumn in primates seems to be constant ([17], their Figure 4A), and instead of making modules smaller, the number of pinwheels per hypercolumns approaches the universal constant π across all species presenting them [14,17,49]. The choice of layout also does not seem to depend on a

critical absolute number of neurons in V1 because agoutis seem to have a number of V1 neurons comparable to or higher than some of the species with maps [39].

Because there exist now only two basic settings, periodic columnar or interspersed, the predictive value of other biological signatures can be reexamined. Jang et al. (2020) proposed that numeric cortical and retinal parameters alone would not predict functional organization, nor would visual acuity. Indeed, agoutis have small receptive fields and highly orientation-selective neurons. Of note, pigeons exhibit considerable visual acuity but an interspersed layout favoring vertical contours [50]. By considering then both retina and V1 size in their functional layout model, the authors claim that a high retino-cortical mapping ratio (V1/R) would predict a columnar layout. Since this ratio is $320 \text{ mm}^2 / 500 \text{ mm}^2$ [51], 0.64, higher than for the tree shrew (0.6), an orientation map would have been predicted for agouti, as well as a noncolumnar layout for the mouse lemur with a V1/R ratio of 0.4 [17], a hypothesis that can also be refuted (Figure 3A).

Figure 4



Orientation selectivity in rodents is not stable across different spatial frequencies. Neurons in the primary visual cortex of rodents [22,79] but not cats [22,83] change their orientation selectivity of $\sim \pm 30\text{deg}$ when doubling the spatial frequency of the grating stimulation. Example polar tuning curve from two single orientation-selective neurons, in agouti V1 (left), and in cat area 17 (right). Figures reproduced with permission from Elsevier. The model of Pattadkal et al. explains these shifts occur with random convergence of inputs of different orientations to neurons in rodent V1 as opposed to iso-orientation selective connectivity in cats. Schematic insets reproduced from Ref. [79].

What factors might still be considered relevant for adopting one of the two distinct layouts?

While absolute numbers appear not to be relevant determinants, neuronal surface density might be. Big rodents have lower neocortical neuronal densities than primates [52,53]. Accordingly, agoutis have lower V1 surface density than primates and carnivores with similar or smaller cortex and body sizes [54] (Figure 3B). This is because rodents increased their cortex with a higher power function exponent than primates [55], leading to relatively lower cell densities and more white matter [56]. Nevertheless, the agouti - in contrast to the world's largest rodent, the capybara - has a high encephalization quotient and the highest neuronal quotient of that order known today [57]. Basically, it contains more (neocortical and cerebellar) neurons than would appear to be required to control a rodent of that size. Due to this relative excess of neurons, agouti could have helped to answer the question of whether any rodent might express a periodic orientation map when the brain size, the neocortical area corresponding to V1, and neuronal density converge towards a critical triplet of features, but there appears to be no rodent outlier. Thus, phylogeny seems to matter.

It is widely accepted that primates and rodents can be classified into the subclade of Euarchontoglires, which combine Glires (rodents, lagomorphs) and Euarchonta (primates, Scandentia, and Dermoptera). The new

data reinforce the evidence that Glires share a common architecture that is different from that in the Euarchonta. In fact, periodic maps appear in all mammalian clades, likely even in a marsupial, *Macropus eugenii* [58], as well as in the barn owl's Wulst [59]. This could be interpreted as a form of convergent evolution of the analogous 'pinwheel' phenotype as an adaptation to a common visual environment. Indeed, those species split off from one another well before the diversification of Eutheria [60]. What renders the Glires different? Apparently, the split of the Euarchontoglires clade before the Cretaceous-Paleogene-boundary 65 mya was followed by bigger effects on primate than rodent brain evolution. This interpretation is based on the finding that younger genes, which seem to be involved with neocorticalization and result of a positive selection for brain functions, emerge in fetal or infant's primates but not rodent brains [61]. Along this line, it is plausible to argue that the salt-and-pepper layout might actually be the layout of the common ancestor. Possibly, primates, including humans, benefited from the neocortical expansion with high visual acuity [53], among other functions, because the new genes increased neuronal density in V1 in primates by up to 2.5 times more than in Glires.

However, other features typical for primates like frontal eyes, binocular overlap (and high visual acuity) seem to be only loosely correlated with the columns- and pinwheel layout (Figure 3C) since ferrets and tree

shrews have eyes located more laterally than even mice, and possess a mixed retinal layout of area centralis and visual streak (for review [35]), which seems to hold also for nocturnal primates like the mouse lemur [62]. Overall, apart from being a Glires or not, a good predictor of cortical layout appears to be the central-to-peripheral (CP) ratio of retinal ganglion cell density as proposed by Ibbotson and Jung [35]. Mouse lemur, with a CP ratio of 22, as well as agouti, with a CP ratio of 2.9, are consistent with this proposition (Figure 3D).

Note, however, that this ratio is not independent of phylogeny! Glires have small CP ratios because their retina contains a visual streak. In most such cases, this predicts a horizontal bias in orientation selectivity (Figure 2). Notably, ground-dwelling and mouse-related Rodentia (rat [63], mouse [64], grasshopper mouse [20], hamster [65], Lagomorpha (rabbits [66], Murphy and Berman, 1979), as well as the investigated Hystricomorpha (agouti leporina [22], their Figure 6D) exhibit this bias (Figure 2). Neurons preferring vertical contours seem necessary to enable stereopsis [67], and those neurons, especially binocular ones, are underrepresented when retinal coordinates become incongruent by eye rotation or strabismus [68,69]. They are potentially also less relevant with lateral eyes. The visual streak of lateral retinas naturally benefits the representation of horizontal over vertical orientations in the arrangement of ON and OFF inputs and biases to horizontal orientation selectivity within the retina already. Although cortical orientation selectivity in rodents seems to result from the alignment of thalamocortical afferents, a strong horizontal bias within the retino-geniculo-cortical loop might combine with the cortical distribution (Figure 2).

In support of this argument, the direction selectivity of postsynaptic cortical neurons in mice correlated well with the spatial displacement of excitatory and inhibitory presynaptic inputs [70]. A report from tree shrews established even further that the smooth representation of orientation, absolute spatial phase, and retinotopy in these animals resulted all from the distinct spatial arrangement of ON and OFF inputs. This arrangement did not only seem to predict cortical orientation preference but also to instruct periodic columnar orientation maps [71]. Accordingly, local tuning biases inherited from the retina might guide or restrict the layout of orientation selectivity [72,73], but see Ref. [74]. However, although targeted manipulation of visual experience through stripe rearing can lead to new biases in orientation preference (e.g. Ref. [75]) and can change spatial interdependencies of different map features [76], it does not erase a columnar layout. Probably, this is because it is seeded prenatally. A strong orientation bias per se would not impair the formation of columns in species, which otherwise can express them. Rather, the strong bias in the retino-geniculo-cortical input taken together with other phylogenetically determined

structural constraints, such as surface neuron and mini-column packing density or astrocytic arbor range [36], might have fixed the potentially ancestral salt- and pepper layout in all Glires independent of size or habitat. Likewise, the close examination of several species in the lineages in which the columns-and-pinwheels layout appeared, i.e. the Euarchonta and Laurasiatheria, points to only little interspecies differences indicating morphological stability [14,17,49] and the high conservation of each layout throughout orders. This could mean that the columns-and-pinwheels layout appeared in the form of a punctual evolutionary change — reminiscent of the debated punctuated equilibrium states of evolution originally proposed by Ref. [77] — and coincident with the separation of these lineages followed by speciation. This hypothesis can be further addressed by comparing species, which are phylogenetically closer to potential common ancestors.

Conclusions and perspectives

In summary, two newly investigated and with regard to the brain in their lineage extreme taxa confirm that the spatial layout of orientation-selective neurons in the primary visual cortex adopts one of two distinct architectures, either salt-and-pepper or columns-and-pinwheels. Neither the large rodent agouti nor the small primate mouse lemur seems to differ much from their relatives of the same order, despite enormous differences in V1 and body size, lifestyle, absolute neuron numbers, binocular overlap, and cortex-retina ratio, indicating that these layouts are highly conserved.

Interestingly, the rodent regions of salt-and-pepper seem to intermingle with mini-columnar structures of roughly similar orientation preference [78,20]. Although unlikely, it is thus possible that a not yet understood (larger) periodicity in the spatial representation of orientation-selective neurons in rodents escaped the scope of previous experiments, see also [25]. Systematic scanning of fine-scale and large-scale functional layouts in large rodents would be necessary to elucidate this question. It is worth noting that, in contrast to what is observed in carnivores, rodent orientation preference is not stable across different spatial frequencies (Figure 4) [79]. This is also confirmed by our work comparing orientation-selective responses at different spatial frequencies in agouti and cat V1 ([22], Figure 7). According to the model proposed by Pattadkal et al. [79], the shift in preference orientation from low to higher spatial frequencies can be obtained even when assuming random connectivity. However, new tract-tracing and recording techniques elucidating the anatomical and functional characterization of intracortical circuits in mice revealed that like-to-like [33,71,80,81], as well as coaxial selectivity [70,82], seem to also dominate the intrinsic connections of rodents. Still, rodent horizontal circuits are supposedly not patchy and differ spatially from those observed in animals with ordered orientation

maps ([32], their Figure 4b). Furthermore, evidence increases that mice V1 integrates over large visual field distances [82] and receives manifold nonvisual inputs (for review, 32). Thus, the hypothesis that rodent circuits process visual objects differently than primates or carnivores is likely. In support, recent behavioral work describes different scene segmentation strategies for primates than for mice [83]. This might imply that the reorganization of visual cortical circuits in primate brain evolution was not functionally neutral.

CRedit author statement

Schmidt KE: Conceptualization, Investigation, Methodology, Data Curation, Visualization, Writing. **Wolf F:** Conceptualization, Writing-Reviewing.

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Conflict of interest statement

Nothing declared.

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