

Scaling of Neuron Number and Volume of the Pulvinar Complex in New World Primates: Comparisons with Humans, Other Primates, and Mammals

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ABSTRACT

The lateral posterior nucleus and pulvinar (LP-pulvinar complex) are the principal thalamic nuclei associated with the elaborate development of the dorsal and ventral streams of the parietal cortex in primates. In humans, a novel site of origin for a subpopulation of pulvinar neurons has been observed, the ganglionic eminence of the telencephalon. This additional site of neuron origin has been proposed to contribute to the pulvinar's evolutionary expansion (Letinic and Rakic [2001] *Nat Neurosci* 4:930–936). Studies of neuron number in the LP-pulvinar complex in gibbon, chimpanzee, and gorilla compared to humans, however, did not show that the human LP-pulvinar was unexpectedly large (Armstrong [1981] *Am J Phys Anthropol* 55:369–383). Here we enlarge the allometric basis for comparison by determining neuron number in the LP-pulvinar complex of six New World primates (*Cebus apella*, *Saimiri ustius*, *Saguinus midas niger*, *Alouatta caraya*, *Aotus azarae*, and *Callicebus moloch*) as well as measuring LP-pulvinar volume in a further set of 24 species including additional primates, carnivores, and rodents. The volume of the LP-pulvinar complex scaled with positive allometry with respect to brain volume across all species examined. The scaling of the number of neurons in the LP-pulvinar complex was extremely similar in New World primates and anthropoid apes, with the human LP-pulvinar value close to the regression line. Comparison of the relative volumes of the LP-pulvinar in the larger sample confirmed this observation, and further demonstrated that both primates and carnivores showed a “grade shift” in its size compared to rodents, with the pulvinar comprising a greater proportion of total brain volume across the board. Diurnal, nocturnal, or crepuscular niche did not discriminate LP-pulvinar size across taxa. *J. Comp. Neurol.* 504:265–274, 2007.

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The pulvinar and lateral posterior complex (LP-pulvinar complex) comprises a number of thalamic nuclei that provide the input to posterior parietal and inferotemporal cortex, cortical regions that become particularly large and differentiated in primates (Van Essen et al., 2001). These areas are critical for some of primates' most central capacities, including visuospatial operations, object and conspecific recognition, and directed attention. Shipp (2004) proposed that the pulvinar acts as a “remote hub for coordinating spatial activity within multiple cortical visual maps” (see also Robinson and Petersen, 1992; Grieve et al., 2000). At a minimum the LP-pulvinar complex thus serves the brain to identify and focus attention on a particular object or task.

Phylogenetically, the pulvinar is thought to be derived from varying embryonic origins in the rodent, in nonhu-

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man primates, and in humans. The same general region of the thalamus that projects to posterior parietal and inferotemporal cortex gives rise to the lateral posterior nucleus in rodents, and the pulvinar-LP complex in primates, although novel regulatory genes are expressed in the primate pulvinar (Altman and Bayer, 1989; Jones and Rubenstein, 2004). The terminology should not suggest that all species have a conserved "LP" while the pulvinar is added in only some species, as both LP and the pulvinar undergo reorganization in primates. Very general thalamocortical mapping rules between LP-pulvinar and posterior cortex hold across all species studied (Mason, 1978; Mason and Groos, 1981; Stepniewska and Kaas, 1998). The multiple subnuclei of the primate LP-pulvinar complex and multiple cortical areas produce a complex and overlapping pattern of projections, however, in which cytoarchitectonic borders and topographic maps often misalign (Gattass et al., 1978; Brysch et al., 1990; Höhl-Abrahão and Creuzfeldt, 1991; Cusick et al., 1993; Gutierrez et al., 1995; Soares et al., 2001; Shipp, 2004; Kaas, 2007). In human development alone, the pulvinar (along with multiple other nuclei of the dorsal thalamus) receives extra GABAergic cells migrating from a telencephalic structure, the ganglionic eminence (Rakic and Sidman, 1969; Ogren and Rakic, 1981; Letinic and Rakic, 2001). These data have been interpreted as support for a "novel and specific mechanism for the co-evolution of brain structures" that in this case led to the evolution of an enlarged human thalamus together with an enlarged parietal cortex (Rao and Wu, 2001).

No quantitative allometric data, however, show that the human pulvinar is unpredictably large. On the contrary, a study of lesser apes, great apes, and humans showed the number of neurons in humans to be allometrically predictable, considering either the entire LP-pulvinar complex or the pulvinar or LP nucleus separately (Armstrong, 1981). Since in any study of great apes the number of animals sampled is necessarily small and tissue origins variable, to demonstrate any difference would require a fairly extreme disparity between humans and the great apes. Thus, one of the aims of the following analysis was to systematically examine the scaling of the LP-pulvinar complex in more extensive samples of both primates and nonprimates in order to better determine if the LP-pulvinar complex may scale differently in various mammalian radiations. We determined neuron number in the pulvinar for six New World primates, as well as computed volumes for a variety of additional species, to allow contrasts between humans, great apes, and primates generally, and primates versus other mammals. A preliminary report of these investigations has been made (Silveira et al., 2005).

MATERIALS AND METHODS

The present article integrates data on neuron number and volume in the pulvinar/LP complex in mammals from a number of sources, including 1) new stereological assessments of neuron number in a number of New World primates from tissue processed directly in our own laboratory; 2) the "Brain Museum" database (<http://brainmuseum.org/sections/index.html>. Access date: 01/05/2006); and 3) brain atlases (Dua-Sharma et al., 1970; Loskota et al., 1974; Stephan et al., 1991; Bons et al., 1998; Morin and Wood, 2001; Paxinos, 2004) and from

various published works (Table 1). A central goal was to ensure the comparability of the various assessments of neuron number and pulvinar, thalamus, and brain volume from these various sources, while being as inclusive as possible. Much effort was made to collect as wide a range of brain sizes and niches as possible, both across the mammalian order and within various mammalian suborders. The most data were available for primate, carnivore, and rodent suborders.

Stereological determination of neuron numbers and volumes of New World monkey brains from sectioned material

Histological procedures. Samples came from animals bred or housed in the Centro Nacional de Primatas in Pará, Brazil. All animal housing and procedures complied with the principles defined in the NIH *Guide for the Care and Use of Animals*, as certified through the IACUC at Cornell University as part of a larger study. Three capuchin monkeys (*Cebus apella*), one squirrel monkey (*Saimiri ustius*), one tamarin monkey (*Saguinus midas niger*), two howler monkeys (*Alouatta caraya*), two owl monkeys (*Aotus azarae*), and one dusky titi monkey (*Callicebus moloch*) were collected from this source.

Animals were dark adapted for 30 minutes, while lightly anesthetized with an intramuscular injection of a 1:4 mixture of 2% xylazine hydrochloride and 5% ketamine hydrochloride. They were then deeply anesthetized with the same mixture and perfused with a phosphate-buffered saline solution (PBS, pH 7.2). An unfixed eye was then removed. They were then perfused with 4% paraformaldehyde. Brains were dissected out and weighed. After 1–2 weeks the brains were placed in 2% paraformaldehyde and refrigerated if extended storage was intended. For sectioning, brains were then sunk in 30% sucrose/PBS (0.1 M; pH 7.2), and sectioned coronally on a freezing microtome at 60 μm . Every fifth or seventh section was mounted on gelatinized slides and stained with cresyl violet.

Determination of volumes and neuron numbers. Volumetric measurements of the pulvinar, thalamus, and whole brain were reconstructed using the Stereoinvestigator program (NeuroLucida, MicroBrightField, Colchester, VT, v. 5). For the pulvinar, seven equally spaced sections were selected for counting, with the exception of one monkey, *Saguinus midas niger*, in which only five were traced. For whole brain volumes a minimum of 14 equally spaced sections were traced. To determine total pulvinar neuron number, we first used the optical fractionator procedure (Stereoinvestigator, MicroBrightField) to determine the number of sites to be counted to reach a coefficient of error of 0.05 or lower, and to locate sampling sites in each section. All counts were done at 750 \times magnification. Section areas were integrated by the Cavalieri method as implemented in Stereoinvestigator and multiplied by neuronal densities per section to determine the total number of neurons per nucleus. All counts were done unilaterally and doubled to represent the volume and total number of neurons in the LP-pulvinar per brain (Table 1; Quantification method Q-3; Table 3). We did not correct for shrinkage on a section-by-section basis, assuming the registration of the volumes of all of the sections counted to total brain volume would effectively average out this type of variation.

TABLE 1. Species, Brain, and PuLP Volumes, Source, Processing, and Classification

| Animal | Scientific Name | SO | Brain Vol (mm ³) | PuLP Vol (mm ³) | T | Q | N |
|-------------------|-------------------------------|----|---------------------------------|--------------------------------|---|---|---|
| Agouti | <i>Dasyprocta agouti</i> | 1 | 15125.48 | 35.68 | F | 3 | D |
| Beaver | <i>Castor canadensis</i> | 13 | 43436.29 | 126.40 | C | 2 | N |
| Cat | <i>Felis catus</i> | 5 | 24710.42 | 123.59 | C | 2 | C |
| Capuchin monkey | <i>Cebus apella</i> | 1 | 60810.81 | 588.06 | F | 3 | D |
| Dog (beagle) | <i>Canis familiaris</i> | 13 | 69498.07 | 334.23 | F | 1 | C |
| Gerbil | <i>Meriones unguiculatus</i> | 12 | 1110.04 | 1.64 | C | 1 | D |
| Gibbon | <i>Hylobates lar</i> | 4 | 101158.30 | 630.92 | F | 5 | D |
| Gorilla | <i>Gorilla gorilla</i> | 4 | 521235.52 | 2819.12 | F | 5 | D |
| Hamster | <i>Mesocricetus auratus</i> | 5 | 965.25 | 1.48 | F | 1 | N |
| Harbor seal | <i>Phoca vitulina</i> | 3 | 238968.15 | 632.88 | C | 2 | D |
| Howler monkey | <i>Alouatta caraya</i> | 1 | 57528.96 | 305.35 | F | 3 | D |
| Human | <i>Homo sapiens</i> | 11 | 1334942.08 | 3560.04 | P | 1 | D |
| Hyena | <i>Crocuta crocuta</i> | 3 | 139131.27 | 729.31 | C | 2 | N |
| Kangaroo | <i>Macropus fuliginosus</i> | 5 | 54054.05 | 212.94 | C | 2 | D |
| Lion | <i>Panthera leo</i> | 3 | 229507.72 | 1015.45 | C | 2 | N |
| Macaque | <i>Trichechecus manatus</i> | 2 | 91698.84 | 717.64 | C | 2 | D |
| Manatee | <i>Trichechecus manatus</i> | 3 | 281888.03 | 2203.04 | C | 2 | C |
| Mandrill | <i>Mandrillus sphinx</i> | 2 | 153861.00 | 1047.71 | C | 2 | D |
| Marmoset | <i>Callithrix jacchus</i> | 6 | 6920.85 | 68.09 | F | 3 | D |
| Mongoose | <i>Cynictus penicillata</i> | 8 | 9652.51 | 142.65 | C | 2 | D |
| Mongoose lemur | <i>Eulemur mongoz</i> | 2 | 21042.47 | 130.46 | C | 2 | C |
| Mouse | <i>Strain C57BL/6J</i> | 9 | 444.05 | 0.81 | F | 4 | C |
| Mouse lemur | <i>Microcebus murinus</i> | 10 | 1709.36 | 15.27 | F | 4 | N |
| Owl monkey | <i>Aotus sp.</i> | 1 | 17374.52 | 128.04 | F | 3 | N |
| Paca | <i>Cuniculus paca</i> | 1 | 31795.37 | 41.30 | F | 3 | N |
| Rat | <i>Rattus rattus</i> | 5 | 1833.98 | 7.42 | F | 1 | N |
| Rock hyrax | <i>Procavia capensis</i> | 7 | 15926.64 | 81.87 | C | 2 | D |
| Sea lion | <i>Zalophus californicus</i> | 3 | 383713.32 | 5288.38 | C | 2 | D |
| Squirrel monkey | <i>Saimiri sciurus</i> | 2 | 23552.12 | 269.70 | F | 3 | D |
| Tamarin | <i>Saguinus midas</i> | 2 | 10038.61 | 87.12 | F | 3 | D |
| Titi monkey | <i>Callicebus moloch</i> | 2 | 18339.77 | 178.76 | F | 3 | D |
| White-tailed deer | <i>Odocoileus virginianus</i> | 3 | 114586.87 | 822.66 | C | 2 | D |
| Zebra | <i>Equus burchelli</i> | 3 | 427944.98 | 2749.68 | C | 2 | D |

SO: Source for brain weight value:

1. This study. 2. Rowe (1996). 3. Reep et al. (2007). 4. Armstrong (1981). 5. Allison and Cicchetti (1976). 6. Stephan et al. (1981). 7. Yom-Tom (1993). 8. Gittleman (1995). 9. Seecharan et al. (2003). 10. Bons et al. (1998). 11. Mai et al. (1997). 12. Cabana et al. (1990). 13. <http://staff.washington.edu/chudler/facts.html> Accessed 08/05/2006.

T, tissue processing: F, frozen sections; C, celloidin; P, paraffin.

Q, quantification technique: 1, atlas; 2, Brain Museum; 3, this study; 4, special process for truncation; 5, volume recovered from cell number.

N, niche: C, cathemeral; N, nocturnal; D, diurnal.

Determination of pulvinar, thalamus, and brain volumes from Brain Museum data, atlas, and literature sources

Criteria for including animals from these sources included the following. All brains had to have no less than five sections containing LP-pulvinar complex, and a minimum of 14 sections spanning the rostrocaudal extent of the brain. All brain images obtained from the brainmuseum.org website had to be of adequate resolution to discern the relevant detail necessary to draw the boundaries of the LP-pulvinar complex. Finally, fresh brain volumes of the specimen were required, preferably obtained from the atlas or laboratory responsible for processing the brain in question.

Images of brains obtained from brainmuseum.org were first saved as JPEG files and then either printed out and traced into NIH Image v1.61 with a Wacom 6 38-in data tablet or loaded into NIH image J 1.31. Using the scaling provided on the site, we estimated the areal extent of each section containing the LP-pulvinar complex, lateral geniculate nucleus (LGN), and using the section thicknesses obtained from the site holders we used Cavalieri's estimator to estimate the volume of the pulvinar, thalamus, and brain (Table 1; Quantification method Q-2).

Correcting for histological shrinkage. All volumes derived from sections, atlases, or web resources were corrected to represent a fraction of whole brain volume by the following procedure. First, the volume of the fresh brain was divided by the volume of its serial-section reconstructed counterpart to obtain a shrinkage correctional

factor. This factor was then multiplied by the volumes of the section reconstructions of the nuclei of interest (e.g., LGN, LP-pulvinar complex, SC) to yield corrected structure volumes. In the case of the domestic dog, the marmoset, and the human brain the authors noted the degree of shrinkage and provided the correctional factor themselves.

Brain volume is related to brain weight by the following equation (Stephan et al., 1991):

$$\text{Volume of Fresh Brain} = \text{Weight of Fresh Brain} \cdot 1.036$$

Whenever possible, fresh brain weights were obtained directly from the atlases, or in the case of fresh tissue from measurements from each animal prior to sectioning; in the few cases where an individual fresh brain weight was not available, the appropriate measurement was obtained from an encyclopedic source (i.e., Stephan et al., 1981). Table 1 contains brain volumes of the animals in our study, along with the sources of brain weights (Table 1; SO). While all of the analyses performed here are expressed as volumes, it is by correcting measured brain volumes by brain weights that allows comparison of the brains from diverse sources to be made.

Of the 30 brains in the dataset, 13 were prepared using the frozen sections (mean shrinkage = 26.4%, Minimum = 0%, maximum = 50.8%, n = 11). Two of these (the mouse and mouse lemur) required special estimation techniques because of absent brain parts, described in the following paragraph. Another 16 were prepared using celloidin em-

TABLE 2. Comparison of Lateral Geniculate Volumes Obtained in the Present Study with Stephan (1981)

| Name | Source | Br (cm ³) (Current) | Br (cm ³) (Stephan) | LGN (mm ³) (Current) | LGN (mm ³) (Stephan) |
|---------------------------|--------|------------------------------------|------------------------------------|-------------------------------------|-------------------------------------|
| <i>Homo sapiens</i> | Atlas | 1334.94 | 1251.85 | 406.69 | 416 |
| <i>Saimiri sciurus</i> | Fresh | 23.55 | 22.57 | 67.52 | 62.9 |
| <i>Aotus sp.</i> | Fresh | 17.37 | 16.19 | 32.33 | 32.9 |
| <i>Callicebus moloch</i> | Fresh | 18.34 | 17.78 | 40.67 | 54.2 |
| <i>Alouatta caraya</i> | Fresh | 57.53 | 49.01 | 99 | 87.4 |
| <i>Saguinus midas</i> | Fresh | 10.04 | 9.57 | 40.07 | 36 |
| <i>Callithrix jacchus</i> | Atlas | 6.92 | 7.24 | 23.16 | 25.1 |
| <i>Macaca mulatta</i> | BrMus | 91.7 | 87.9 | 190.11 | 158 |
| <i>Cebus apella</i> | Atlas | 60.81 | 66.94 | 116.44 | 137 |

bedding (mean shrinkage = 68%, minimum = 51.7%, maximum = 82.5%, n = 16), and the remaining human brain was prepared using paraffin embedding.

The atlases of the mouse lemur brain (*Microcebus murinus*; Bons et al., 1998) and the mouse (*Mus musculus*) truncate large parts of the olfactory bulb, frontal lobe, cerebellum, and brainstem (Table 1, Quantification method Q-4). Although this missing volume of tissue precludes obtaining brain volumes in the usual way using Cavalieri's estimator, pulvinar and brain volumes could be approximated in the following manner. First, uncorrected LP-pulvinar complex, LGN, and thalamus volumes were obtained from serial section reconstruction in the usual manner. The discrepancy between the uncorrected volume of the LGN and that of the fresh-tissue volume of the same structure provided by Stephan et al. (1981) was determined and applied to the volumes of the LP-pulvinar complex and total thalamus. Finally, to account for a slight discrepancy (4%) in brain size between the atlas specimen and Stephan's, the volumes of each of LGN, and LP-pulvinar complex were multiplied 1.04% to obtain the final volumes used in the analyses. The brain of the mouse in our sample was processed in the same way, but with reference to the fresh brain and corrected LGN volumes provided by Seecharan et al. (2003).

To register the data collected by Armstrong (1981) on LP-pulvinar complex neuron counts in great apes with percentage volume of fresh brain weights, the function relating total LP-pulvinar complex cell number to nucleus volume determined in this study was employed (Fig. 3; Table 1 Quantification Method Q-5).

Finally, the choice of what aspect of brain morphology to compare LP-pulvinar volume was dictated by which measure allowed the most comparison with the extant literature. Several options were available: whole brain volume, thalamus volume, thalamus minus LP-pulvinar, or possibly cortex volume. Whole brain volume (whole brain, from the level of the pyramidal decussation in the medulla, including olfactory bulbs) is certainly the most widely used comparison method, and since the pulvinar is a small percentage of whole brain volume, overestimating the predictability of pulvinar scaling because of inclusion of pulvinar volume in brain volume is a minor issue. The extreme predictability of the scaling of each brain part with respect to whole brain (Finlay et al., 1995) can be used to recompute the scaling of LP-pulvinar size with respect to any other brain component if such an analysis would be of interest.

Comparison of the results of this data analysis to published literature values. The unusual diversity of sources for these brain measurements made it desirable to determine whether our correction and quantification

methods were successful in calibrating the brains to each other. Nine of the species we examined, divided between those prepared in our own laboratory and from atlases and databases, are identical to the species, but not the individuals examined by Stephan et al. (1981), the most widely used source in allometric studies (Table 2), but the Stephan studies did not measure the volumes of the LP-pulvinar complex. However, the lateral geniculate nucleus was measured. We therefore measured the volumes of the lateral geniculate nucleus in the nine species we examined using Stephan's cytoarchitectonic criteria, but our own volume-estimation protocol to determine how commensurate the final values are from the two sources.

Cytoarchitectonic criteria for identification of the LP-pulvinar complex

Primate LP-pulvinar complex. The LP-pulvinar complex of primates has been well explored and is delineated clearly (Stepniewska and Kaas, 1998). The lateral posterior component is located posterior to the ventral lateral nucleus, and is flanked superficially by the lateral dorsal nucleus (LD) and the dark staining cells of the ventral basal nuclear complex inferiorly. As one moves posteriorly through the thalamus, the LD nucleus is gradually replaced by the pulvinar itself, a massive, striated complex with medial, lateral, and oral subdivisions that is surrounded by easily identified nuclei such as the central lateral nucleus (CL), LGN, medial geniculate (MGN), and central medial nuclei (Fig. 1). The pulvinar complex continues to extend posteriorly after all other thalamic nuclei have receded and it begins to recede even as the superior colliculus becomes more prominent. Overall, the borders of the primate LP-pulvinar complex presented few cases of ambiguity.

Rodent LP nucleus. Rodents lack an LP-pulvinar complex per se, but retain the LP component of the LP-pulvinar whose projections are characteristic of the LP-pulvinar complex overall in other brains (Mason and Groos, 1981; Höhl-Abrahão and Creuzfeldt, 1991). In rodents, the LP nucleus is small but easily identifiable. This nucleus is located medial of the LD nucleus, lateral to the central lateral nucleus, and below the dentate gyrus of the hippocampus. LP extends posteriorly through the thalamus, gradually moving laterally as the SC grows in prominence. In five of the six rodent brains in our sample, our sources were atlases where the LP borders had been delineated by their authors, and these were used as given. In the remaining rodent, the beaver, LP was unremarkable.

Carnivore LP-pulvinar complex. The domestic cat and the domestic dog are the only two carnivores for which complete stereotaxic brain atlases exist. The LP-pulvinar complex nucleus of the terrestrial carnivores (domestic

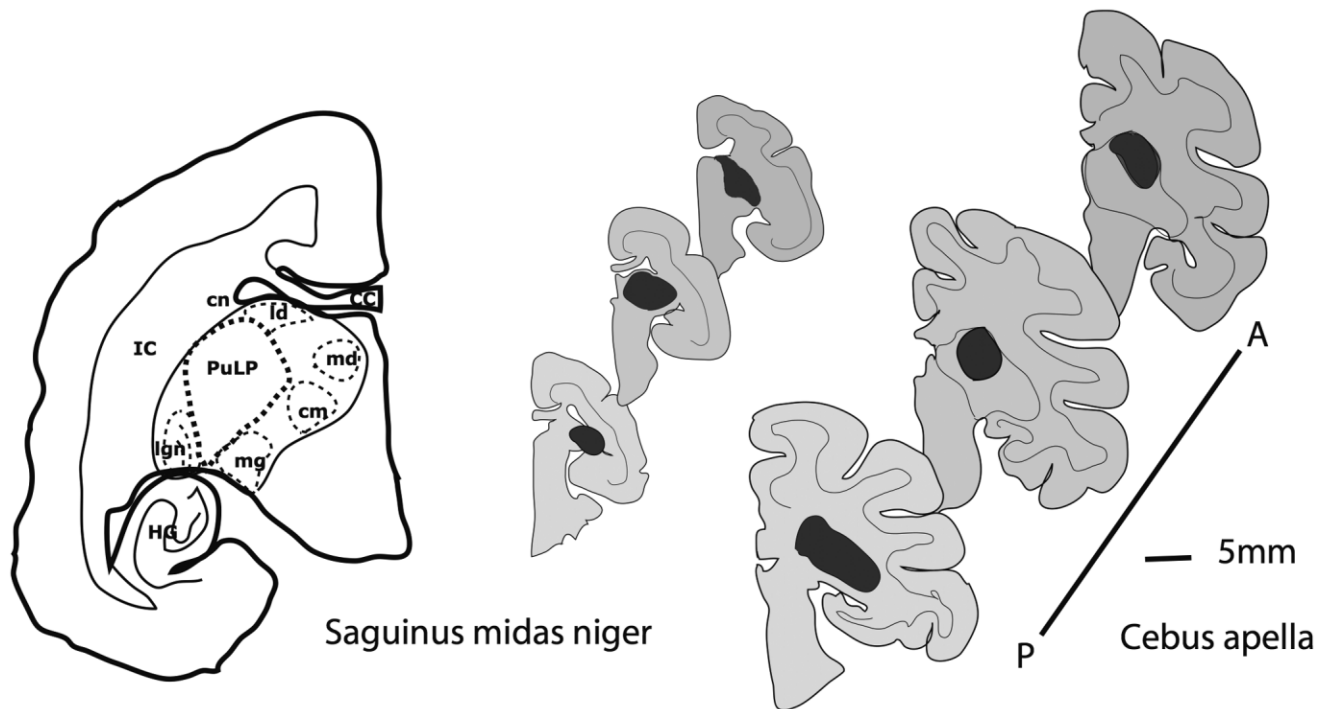


Fig. 1. Three tracings of the brain and LP-pulvinar complex in *Cebus apella* (right) and *Saguinus midas niger* (center) to illustrate the relative size range of pulvinar and brain in this sample of New World monkeys. The three sections traced span 1.8 mm in *Saguinus* and 4.2 mm in *Cebus*. On the left, a tracing of *Saguinus*, magnified

3 \times , to show adjacent thalamic nuclei. cm, centromedial nucleus; lg, laterodorsal nucleus; lgn, lateral geniculate nucleus; md, mediodorsal nucleus; mg, medial geniculate nucleus. Also, CC, corpus callosum; HG, hippocampal gyrus; IC internal capsule.

cat, dog, mongoose, hyena, African lion) and to a lesser degree marine carnivores (harbor seal and sea lion) in our sample were similar enough in organization to allow use of the cat atlas as a model, albeit with somewhat less certainty than for primates and rodents. In these carnivores, as in primates, the LP nucleus is located just below the LD nucleus and lateral to the CL complex. The LP nucleus expands medially as it proceeds posteriorly, and the pulvinar complex gradually displaces the LD nucleus. This complex typically extends posteriorly until the pretectum becomes prominent.

LP-pulvinar complex in other mammalian orders. For suborders for which there were no stereotaxic atlases or published anatomical descriptions of dorsal thalamus consistent identification of all parts of the LP-pulvinar complex was the most difficult (e.g. zebra, rock hyrax, manatee). Nevertheless, because the structures that bound the LP-pulvinar complex (LD, LGN, MGN) are usually recognizable, and because the pulvinar nucleus retains a characteristic morphology, the borders of the LP-pulvinar complex for these animals can be defined with reasonable confidence, although with somewhat less confidence than the rest of the dataset.

Statistical analysis

In order to determine the relative importance of mammalian order in predicting pulvinar number and volume, we employed a stepwise regression using niche, mammalian order, brain size, and all two-way interactions of these as predictor variables. For comparisons of nocturnal,

diurnal, and cathemeral niche on LP-pulvinar complex volumes, the method of independent contrasts was used (Purvis and Rambaut, 1995), using a fully resolved phylogenetic tree with branch lengths set to equal.

RESULTS

Calibration of the present quantification techniques with the published literature

While the scaling of the pulvinar has only been studied quantitatively in great apes, the volume of the lateral geniculate has been measured in a number of studies, notably those by Stephan and associates. These studies offer an opportunity to determine if the corrections for the various types of tissue processing and volume calculations return similar volumes in these separate allometric analyses. These results are listed in Table 2 and graphed in Figure 2. The results are extremely similar, particularly considering the multiple sources of the new data. The regression equation for LGN versus brain volume in the nine species measured by Stephan is $y = 0.5561x + 0.9998$ ($R^2 = 0.9396$), while the results of the present analysis return $y = 0.5611x + 0.9794$ ($R^2 = 0.9118$), thus only slightly and insignificantly more variable, and the plotted regression lines overlay each other in Figure 2.

LP-pulvinar of the New World monkey

The cytoarchitectonics of the LP-pulvinar in the six species examined (*Aotus azare*, *Callicebus moloch*, *Al-*

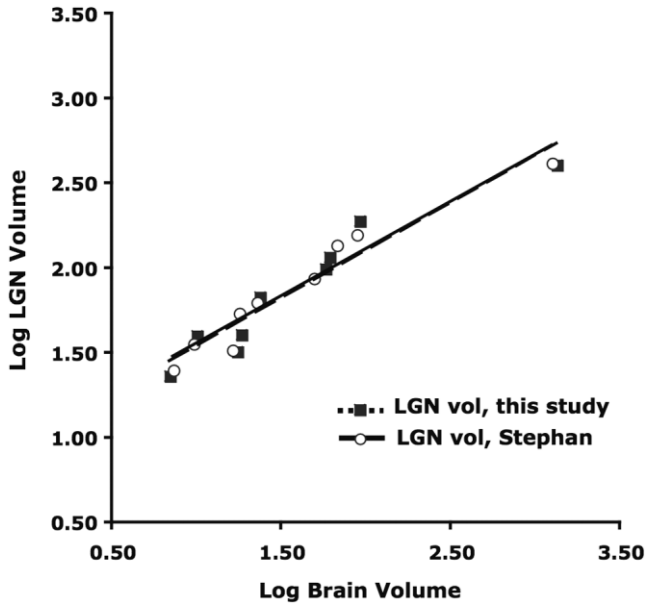


Fig. 2. Scatterplots and regression lines of the relationship of LGN volume to brain volume for nine species of animals measured separately by Stephan et al. (1981) and in the present study (Table 2).

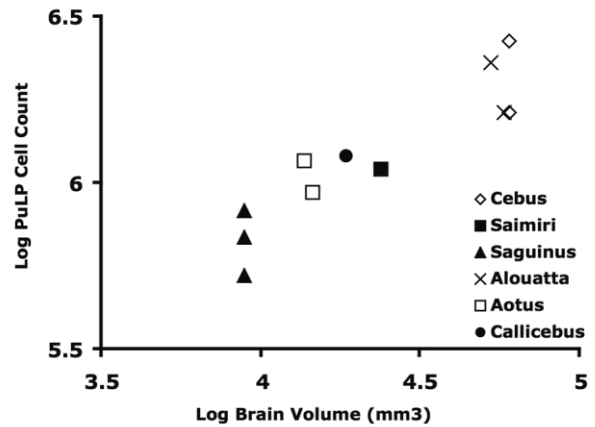
TABLE 3. Pulvinar Complex Cell Counts and Volumes for New World Monkeys

| Species | Sex | ID | Pulvinar Count | PuLP Vol (mm ³) |
|--------------------------|-----|-------------|----------------|-----------------------------|
| <i>Cebus apella</i> | F | Ca970107A | 2,691,519 | 167.68 |
| | M | Ca970913 | 1,633,400 | 133.54 |
| <i>Saimiri sciurus</i> | F | Su960109C | 1,109,219 | 50.34 |
| <i>Saguinus midas</i> | M | Sm970108A | 688,560 | 30.78 |
| | F | Sm970108B | 828,200 | 54.02 |
| <i>Alouatta caraya</i> | F | Sm960111A | 530,086 | 28.00 |
| | M | AC970111A | 2,324,117 | 173.59 |
| <i>Aotus azarae</i> | M | AC970110A | 1,636,957 | 134.29 |
| | F | AA980115A | 1,171,935 | 54.14 |
| <i>Callicebus moloch</i> | F | AA980115 | 947,524 | 62.06 |
| | F | CM 9801108B | 1,212,107 | 62.33 |

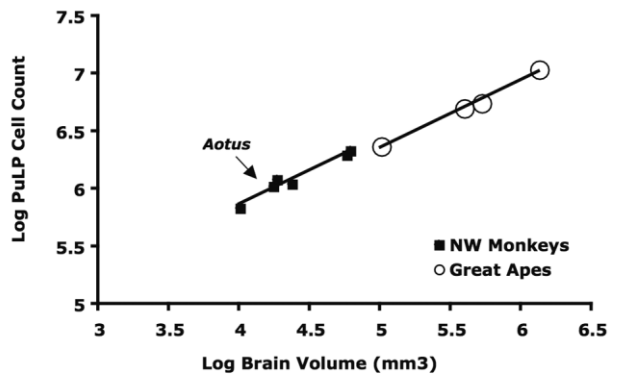
ouatta caraya, *Saguinus midas niger*, *Callithrix jacchus*, *Cebus apella*) revealed no notable differences from those described in prior anatomical characterizations of the primate pulvinar. In the present set, the relative volumes of the pulvinar vary by nearly a factor of 10 (Tables 1, 3), from the smallest *Callithrix* and *Saguinus* to the largest brain in this set, *Cebus apella*. Figure 1 shows anterior, middle, and posterior tracings from the extent of the pulvinar in *Saguinus* versus *Cebus* including a representative middle section.

In these New World monkeys the number of neurons increases as a regular allometric function of brain size (Table 3; Fig. 3A,B). Figure 3A plots the individual animal values as determined in this study, while 3B plots the mean of New World monkey values from this study versus the four species counted by Armstrong (1981), the gibbon, chimpanzee, gorilla, and human, summing the pulvinar and LP numbers determined separately by Armstrong. The regression equation of pulvinar neuron number versus brain size is $y = 0.5866x + 3.5199$; $R^2 = 0.9582$. The regression equation characterizing the slope of LP-

A Individual PuLP Cell Counts, NW Monkeys



B PuLP Cell Counts



C PuLP Cell Density vs Volume

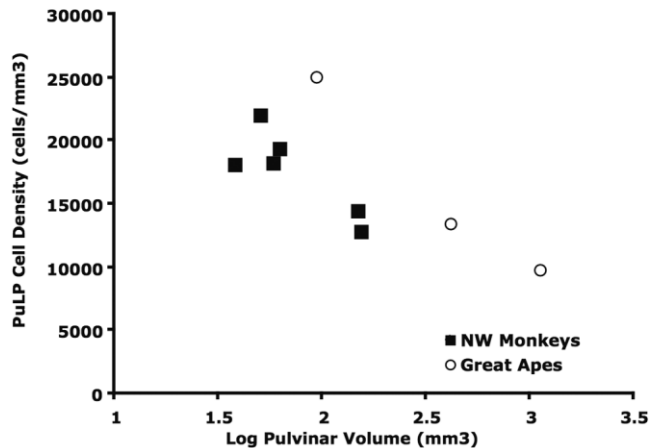


Fig. 3. Graph of the number of neurons in the LP-pulvinar complex for individual New World monkeys versus brain volume computed in this study. Mean neuron number for the LP-pulvinar complex, for the New World monkeys measured in this study versus the great apes (including chimpanzee and human) measured by Armstrong (1981). Inverse relationship of cell density and total LP-pulvinar volume, for New World monkeys and great apes.

pulvinar complex number versus brain volume for great apes, including humans is $y = 0.5876x + 3.4186$; $R^2 = 0.9925$, and that the point for humans, the largest, lies on the regression line. While statistical comparison of these two small groups has little power, the two computed slopes are strikingly colinear. Note also that the value for *Aotus*, the nocturnal owl monkey, does not deviate from that of the diurnal primates.

Finally, reduction in neuronal density within the pulvinar as total brain size and connectional volume increase appears to be continuous across New World monkeys and great apes (Fig. 3C). The continuity of the function relating neuronal number to density enables better comparisons to the analyses concerning volume alone that follow.

Scaling of LP-pulvinar complex volumes across mammalian taxa and niche

In Figure 4A–C the relative volume, as opposed to neuronal number, of the LP-pulvinar complex is plotted for all of the species listed in Table 1 (Fig. 4A). Figure 4B contrasts the scaling of the LP-pulvinar complex by suborder, and 4C contrasts by niche, comparing nocturnal, diurnal, and cathemeral. Across all species, LP-pulvinar complex volume scales slightly positively with respect to total brain volume ($y = 1.0848x - 2.6627$; $R^2 = 0.9186$, $P < 0.0001$).

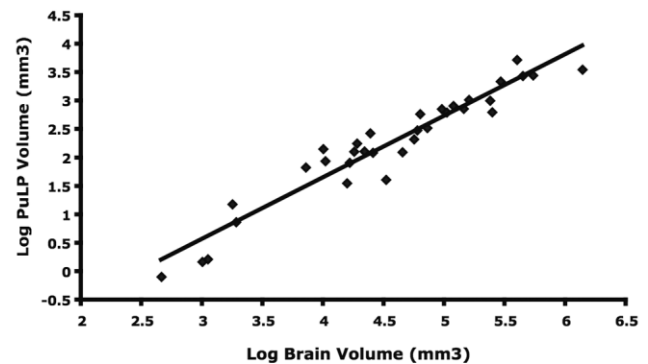
Across the taxa contrasted here, the slope of the regression equations do not differ statistically between any of the groups, while the intercepts differ significantly between rodents and primates (pairwise comparisons, $P < 0.009$), and marginally between carnivores and primates (pairwise comparison, $P < 0.073$). The primate LP-pulvinar complex has a marginally higher intercept than the composite animal slope. For primates, the regression equation is $y = 0.8321x - 1.3719$, $R^2 = 0.9652$; for carnivores, $y = 0.8278x - 1.3627$, $R^2 = 0.7682$; and for rodents $y = 1.025x - 2.7942$, $R^2 = 0.9521$.

When the data are grouped by niche, rather than taxon, no significant differences were found between the nocturnal, diurnal, and cathemeral groups. For diurnal animals the regression equation relating LP-pulvinar complex volume to brain volume is $y = 0.9937x - 2.1676$, $R^2 = 0.8747$; for nocturnal animals, $y = 1.0207x - 2.5172$, $R^2 = 0.906$, and for cathemeral animals, $y = 1.25x - 3.2323$, $R^2 = 0.9954$. After removing the effects of phylogenetic relatedness and of diurnal or nocturnal niche by the method of independent contrasts (CAIC), it was found that brain volume still significantly predicted the size of the LP-pulvinar complex ($F(1,17) = 125.004$, $P < 0.0001$, $R^2 = 0.785$). However, niche did not predict LP-pulvinar complex volume ($F(1,3) = 5.0$, $P = 0.111$). Stepwise regression analysis confirmed these results. Only brain volume and ($F(1,20) = 210.229$, $P < 0.0001$) and order ($F(1,20) = 30.119$, $P < 0.0001$) predicted LP-pulvinar complex volume.

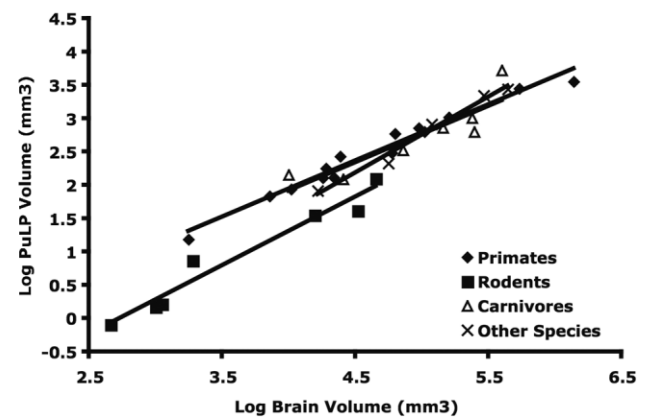
DISCUSSION

Overall, the present results support the argument that the pulvinar scales regularly throughout the primate lineage, showing a “grade shift” between rodents and both carnivores and primates. As we have also shown for the primary and secondary visual cortex, including both number of areas, and cortical area or volume, there are mul-

A PuLP vs Brain Volume



B PuLP Volume by Taxon



C PuLP Volume by Niche

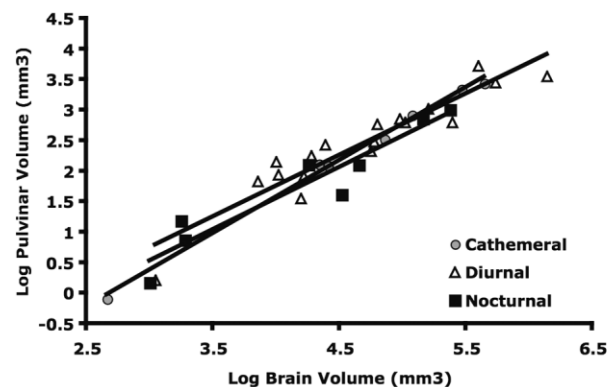


Fig. 4. Overall relationship of LP-pulvinar volume to brain volume for all species collected for this study. Regression relationships for LP-pulvinar volume to brain volume separated by taxon. Regression relationships for LP-pulvinar volume to brain volume separated by niche.

iple differences in scaling of central visual system structures by taxon, but not by niche (Kaskan et al., 2005).

Methodological concerns in quantification of allometric patterns

In the present study we quantified two aspects of scaling in the LP-pulvinar complex, cell number and nucleus

volume, in both cases using stereological techniques adapted to the requirements of primate tissue gathered as a part of a larger study. In the case of neuron number, our principal comparison is with Armstrong's quantification of thalamic neuron number and nuclear volume in great apes (Armstrong, 1979a,b, 1980, 1981), and for nucleus volume the careful reconstructions of Stephan et al. (1981). In both cases the comparability of the numbers generated is quite excellent, even though the Armstrong studies use the geometric "split cell" corrections, not the most preferred in the current literature, and the Stephan studies use a volume reconstruction method slightly less continuous in volume fitting than the Cavalieri method used presently (that is, the Cavalieri method fits a curve to estimate nucleus volume between sections, while the older work fits a straight line). In all cases, registration of all measures to fresh brain weight appeared more than adequate for useful comparison. A great deal of debate has gone on about the best methods for cell and volume reconstructions (Rosen and Harry, 1990; Popken and Farel, 1997; Baddeley, 2001; Guillery, 1997, 2002; Herculano-Houzel and Lent, 2005). We note in the application described here, involving thick sections where cell diameters are considerably smaller than section thickness, over a wide range of brain sizes, the differences between the techniques are demonstrably very small compared to the differences in brain organization of interest.

Is the human pulvinar different from that of other primates?

The convincing demonstration that the human pulvinar contains an embryonic dose of cells from an origin different from macaque monkeys and rodents presents a puzzle. This observation was first suggested by direct observation of tritiated thymidine-labeled material and observation of routes of migration (Rakic and Sidman, 1969; Ogren and Rakic, 1981), and recently confirmed by demonstration of migration in fresh tissue combined with immunocytochemical labeling (Letinic and Rakic, 2001). Moreover, the cells arising from the ganglionic eminence of the telencephalon have been confirmed to be GABAergic interneurons (Rao and Wu, 2001). If the human pulvinar has two sources generating neurons, and other species just one, why do the number of neurons in and volume of the pulvinar in humans lie on the regression line produced by the other species?

For context, we need first to consider what we expect to be the case in scaling overall. Misunderstanding of what the "expected" size of a brain part should be has been a continual source of unnecessary controversy—for example, the human cortex is the size it should be for a primate of our brain size (Finlay and Darlington, 1995), as is the area of our frontal cortex with respect to the rest of the cortex (Jerison, 1997; Semendeferi et al., 2002)—neither are "unusually well-developed" in humans. What predicts what size the cortex, or the frontal part of the cortex, should be? Even though both are a larger percentage volume of the brain, or of the cortex respectively compared to smaller-brained primates, their values need to be compared to allometrically derived predictions and not assumed to be equally proportional. If the appearance of the human pulvinar is compared with animals with smaller brains, it is quite noticeably larger, spilling out over the dorsal thalamus in the "pillow" shape that gives it its name, and it might appear that its size requires special

explanation. In fact, it does not. The pulvinar scales with positive allometry compared to the rest of the thalamus, which means as the thalamus becomes large in any evolving brain, the pulvinar becomes proportionately larger—it does not stay a constant fraction of the thalamus (Armstrong, 1981; present study). In general, structures with positive allometry that become (by definition) "disproportionately" large in large brains have a duration of cyto-genesis that extends later in development than structures with negative allometry. The basic mathematics of the kinetics of variable periods of cell division produce nuclei that enlarge at different exponents (Finlay et al., 1998; Clancy et al., 2001). For example, if the progenitor pools of two cell groups, say the LGN and LP-pulvinar, begin identical in number, but the LP-pulvinar progenitor pool, with its later "birth date" than the LGN, has more cell doublings after the LGN progenitor pool ceases to double, it necessarily becomes larger than the LGN at some exponential value. In addition, neuropil and white matter volume increases at an even greater rate than cell number, in that the connective requirements of larger numbers of cells typically increase at an exponent greater than one (Murre and Sturdy, 1995; Zhang and Sejnowski, 2000), an observation that we confirm in the case of the pulvinar as well (Fig. 3C).

Even with respect to this base prediction, the addition of a completely new source of cells to a nucleus in one species should make its neuron number become even larger than expected even from its positive allometry, and we did not see evidence of this. We should emphasize, of course, that we can make limited statistical claims about these data, as the number of observations of human and other large primate data is small and will remain so. Rather, we are describing the number and nature of the samples so that readers may draw their own conclusions about the likelihood of the conclusion that the human pulvinar is in the range of allometric predictability. The Armstrong observation, for human pulvinar number and an independent assessment of volume, rests on three human samples, two male and one female, all of average brain weight, between 19 and 32 years of age, whose causes of death were unrelated to any brain pathology (Armstrong, 1979). In the present study we used a separate single source for human pulvinar volume for the volumetric analysis, entirely separate from Armstrong's, but which returned a value very close to that she determined (Mai et al., 1997). We also confirm a significant negative relationship of pulvinar size and cell density within great apes and human (Armstrong, 1981), and show a regular scaling of the pulvinar across all of the primates measured with low individual and species variability.

Armstrong (1981) noted that both the human pulvinar and lateral posterior nucleus, unlike that of great apes, has a bimodal distribution of cell volumes consistent with the observations of Rakic and colleagues, suggesting the introduction of a population of small cells accounting for (roughly) 35% of the total cells present; a population of about 30% GABAergic cells in the human thalamus was described consistent with this observation. Subsequent to these studies it has been discovered that these GABAergic cells of telencephalic origin populate all the nuclei of the dorsal thalamus, not only the LP-pulvinar complex (Letinic and Kostovic, 1997). Curiously, however, all of the various nuclei of the human thalamus, whether primary sensory nuclei which have negative allometry with respect

to the thalamus, or the association nuclei with positive allometry, are very well predicted by the data in other primates and do not deviate systematically upward, as would be predicted by a uniform dose of 33% more cells (Finlay and Darlington, 1995).

For a first hypothesis, we could imagine that two separate embryonic events might have occurred to reorganize the human thalamus, a first event reducing the precursor pool for the dorsal thalamus, and a second (numerically) symmetric event in the telencephalon, producing GABAergic cells along with the migratory instruction to place these cells in the dorsal thalamus. More parsimonious, however, is the possibility that a fraction of precursor cells destined for dorsal thalamus in other primates in humans come instead under the organizing influence of the generative regions producing the telencephalon. These cells might proliferate in the telencephalic region where they are specified as GABAergic as a single embryonic fate reassignment, but migrate back to populate their original diencephalic target. This minimizes the total number of genetic changes required. The prosomeric regions giving rise to these regions in the adult roughly adjoin embryonically, so such a reassignment is physically possible (Rubenstein et al., 1994; Reep et al., 2007). The possibility of such a single embryonic reassignment would account for the facts that the human thalamus does not differ from other primate thalami in the times its various nuclei are produced (Clancy et al., 2001), nor in expected cell number, but only the complement of its cell types and the early migratory patterns of the cells.

Independence of pulvinar cell number and volumes from niche

The eyes of nocturnal and diurnal mammals differ substantially in the complement of cones versus rods they comprise, the cells associated with rod and cone pathways in the retina, general topography, and eye size and conformation independent of retinal cell number (Finlay et al., 2005b). Although we might reasonably suspect that a presumed lesser dependence on vision in nocturnal mammals, and greater reliance on other sensory systems, might be reflected in fewer cortical areas or less cortical volume devoted to vision compared to other sensory systems (Barton and Harvey, 2000), surprisingly, this was not the case. As in the present study, the number and volumes of cortical areas scaled with high regularity with brain size, showing no niche-related contributions to variance, along with taxon-related variation in total allocation of mass to cortex versus limbic system (Finlay et al., 2005a; Kaskan et al., 2005). The present study extends this generality to the LP-pulvinar complex, and we plan future studies comparing diverse mammals to explore which subcortical areas vary with retinal organization and niche, and which are independent of them.

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