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Mosaic evolution of brain structure in mammals

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The mammalian brain comprises a number of functionally distinct systems. It might therefore be expected that natural selection on particular behavioural capacities would have caused size changes selectively, in the systems mediating those capacities[1–3]. It has been claimed, however, that developmental constraints limited such mosaic evolution, causing co-ordinated size change among individual brain components[3]. Here we analyse comparative data to demonstrate that mosaic change has been an important factor in brain structure evolution. First, the neocortex shows about a fivefold difference in volume between primates and insectivores even after accounting for its scaling relationship with the rest of the brain. Second, brain structures with major anatomical and functional links evolved together independently of evolutionary change in other structures. This is true at the level of both basic brain subdivisions and more fine-grained functional systems. Hence, brain evolution in these groups involved complex relationships among individual brain components.

Studies of mammalian brain evolution have highlighted the neocortex as a structure associated with intelligence and flexible behaviour, which varies enormously in size between species[4–6]. Large-brained mammals, such as primates, tend to have a neocortex that is disproportionately expanded relative to other structures[3]. The extent to which this size variation can be explained by allometric scaling relative to the rest of the brain, as opposed to size changes independent of other brain structures, remains unclear however[3,7]. Figure 1 indicates clearly that neocortex size varies even after accounting for its scaling relationship with the size of the rest of the brain. The three parallel lines with different intercepts indicate taxonomic differences (grade shifts) in relative neocortex size between primates and insectivores, and, within the primates, between strepsirhine and haplorhine sub-orders. Independent contrasts analysis confirms the presence of significant grade shifts in relative neocortex size. First, the slopes are statistically indistinguishable (haplorhine versus strepsirhine primates: $t = 1.6$, degrees of freedom, d.f. $= 37$, $P = 0.13$; primates versus insectivores: $t = 0.6$, d.f. $= 71$, $P = 0.54$). Second, the absolute values of the contrasts between orders and sub-orders are unusually large and beyond the range of all other contrasts in each data set (haplorhine versus strepsirhine residual = 2.8 standard deviations greater than the mean; primate versus insectivore residual = 5.6 standard deviations greater than the mean). On the basis of separate regression equations for insectivores and primates (averaging between strepsirhines and haplorhines), a primate with a non-neocortical brain size of 1,000 mm^3 would have a neocortex nearly five times larger than would an insectivore with the same non-neocortical brain size (881 mm^3 versus 187 mm^3). In some specific cases, we observe an even greater difference in relative size. For example, the common tenrec *Tenrec ecaudatus*, an insectivore, has a non-neocortical brain volume somewhat greater than that of the

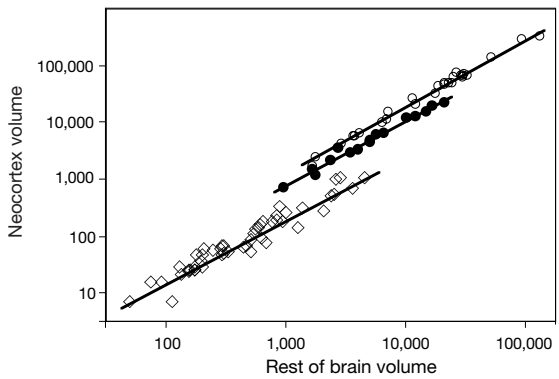

Figure 1 Taxonomic differences in relative neocortex size among primates (strepsirhines and haplorhines) and insectivores. Brain part volumes are in cubic millimetres. Open circles, harplorhine primates; closed circles, strepsirhine primates; diamonds, insectivores. Slopes (and 95% confidence intervals) for insectivores, strepsirhines and haplorhines respectively are 1.11 (1.03–1.20), 1.13 (1.04–1.22) and 1.20 (1.14–1.26).

Table 1 Regression statistics for the scaling of neocortical white and grey matter volume on volume of the rest of the brain

	White matter volume			Grey matter volume		
	Slope	Confidence intervals	r^2	Slope	Confidence intervals	r^2
Insectivores	1.32	1.23–1.41	0.95	1.09	0.94–1.18	0.94
Strepsirhines	1.48	1.32–1.65	0.99	1.06	0.98–1.14	0.99
Haplorhines	1.53	1.37–1.67	0.98	1.12	1.07–1.18	0.99
New World Monkeys	1.40	1.20–1.59	0.98	1.08	0.96–1.21	0.98
Old World monkeys	1.42	0.13–2.71	0.92	0.97	0.45–1.49	0.97

marmoset *Cebuella pygmaea* (2,058 versus 1,770 mm^3), yet the marmoset's neocortex is nearly ten times larger (2,535 versus 273 mm^3). Substantial taxonomic differences in neocortex size thus exist after taking scaling into account. Although the rest of the brain includes the olfactory bulb, which has reduced in primates, the taxonomic differences in neocortex size are still apparent when scaled against non-olfactory structures.

How important are these grade shifts, as opposed to allometric scaling, in explaining the disproportionate expansion of the neocortex in large-brained taxa? Figure 1 indicates that, when the effects of the grade shifts between orders and sub-orders are taken into account, the scaling of neocortex size is nearly isometric (that is, in direct proportion to the rest of the brain, as would be indicated by a slope between log-transformed variables of 1). This indicates that allometric scaling has a relatively small effect on proportional differences in neocortex size. Furthermore, the slight departure from isometry is attributable to the white matter component alone (Table 1). White matter volume of the neocortex scales with marked hyper-allometry relative to the rest of the brain. The white matter consists of fibres connecting neocortical areas to each other and to other structures, and the hyper-allometry is predicted by simple scaling models of connectivity in brains of varying size[8,9]. In contrast, grey matter volume scales isometrically—a conclusion that holds when neocortical grey matter volume is scaled against non-cortical nuclei which themselves have no major white matter component (unpublished analysis of cerebellar and medullary nuclei). Hence, taxonomic differences in the proportion of the brain composed of neocortical grey matter volume are independent of overall brain size (Fig. 2).

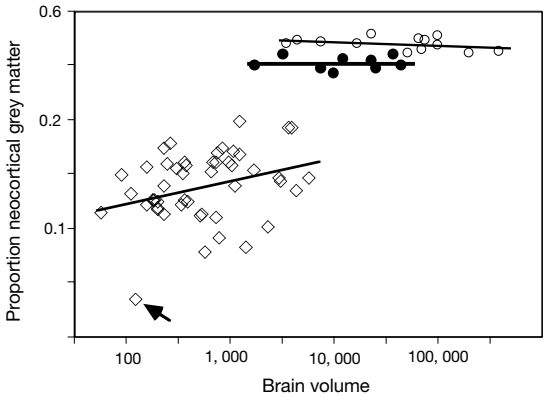

Figure 2 Proportion of brain volume composed of neocortical grey matter in relation to overall brain volume. Symbols as in Fig. 1. The proportion of grey matter is uncorrelated with brain volume in strepsirhines ($r^2 = 0.0004$, $n = 9$, $P = 0.99$), haplorhines ($r^2 = 0.07$, $n = 13$, $P = 0.20$) or the combined primate sample ($r^2 = 0.01$, $n = 22$, $P = 0.28$). The weak positive correlation for insectivores ($r^2 = 0.08$, $n = 48$, $P = 0.03$) becomes non-significant when the outlying species (*Geogale aurita*, arrowed) is removed ($r^2 = 0.04$, $n = 47$, $P = 0.09$). Independent contrasts analysis confirms the lack of association between brain size and proportion of neocortical grey matter (primates: $r^2 = 0.01$, $n = 20$, $P = 0.72$; insectivores: $r^2 = 0.05$, $n = 32$, $P = 0.12$).

Table 2 Correlated volumetric evolution among major brain structures revealed by multiple regressions on independent contrasts

	Diencephalon	Mesencephalon	Cerebellum	Medulla
Primates (n = 40 independent contrasts)				
Neocortex	0.65 (4.06***)	0.05 (0.31)	0.51 (4.54****)	–0.21 (1.80)
Diencephalon		0.43 (3.42**)	0.03 (0.21)	0.13 (1.22)
Mesencephalon			0.02 (0.11)	0.35 (3.15**)
Cerebellum				0.32 (2.33*)
Insectivores (n = 33 independent contrasts)				
	Diencephalon	Mesencephalon	Cerebellum	Medulla
Neocortex	1.12 (4.94****)	–0.19 (0.96)	0.21 (1.24)	–0.16 (0.99)
Diencephalon		0.38 (3.83***)	0.23 (2.35*)	–0.02 (0.88)
Mesencephalon			–0.26 (1.70)	0.52 (4.44***)
Cerebellum				0.43 (2.72**)

Standardized regression coefficients are given with associated t-values and significance levels in parentheses. Structures in the left column were regressed on those in the top row (results are given only above the diagonal because identical t values and P values are obtained when regressing structures along the top row on structures in the left column). Significant t values indicate that the two structures exhibit significantly correlated evolution with the effects of change in the other structures partialled out. ****, $P < 0.0001$; ***, $P < 0.001$; **, $P < 0.01$; *, $P < 0.05$. The patterns of correlated evolution are displayed visually in Fig. 3.

Next we examine the patterns of interrelationships among brain structures. If brain evolution occurred by size change concentrated in specific brain systems, significant correlations should be found between structures linked by important functional and anatomical connections, even after accounting for the effects of size change in other structures. We analysed correlated evolution among brain structures in primates and insectivores, using the method of independent contrasts. The first analysis was restricted to major structures of the mammalian brain, the neocortex, diencephalon, mesencephalon, cerebellum and medulla, to assess whether mosaic evolution is detectable even at this anatomically crude level. The neocortex was included rather than the entire telencephalon, as the latter incorporates structures that vary greatly in functional and connectional properties (some of these are tested in the subsequent analyses). The results (Table 2) are summarized in Fig. 3, and give rise to two main conclusions. First significant partial correlations exist. That is, particular pairs of structures show significantly correlated volumetric evolution even after accounting for the effects of change in the other structures. Second, the patterns of correlated evolution are strikingly similar in the two orders. Of the five significant positive partial correlations in each taxon, four are shared between taxa. The explanation for this resemblance could be fundamental similarities in anatomical and functional connections, common developmental constraints[3,7], or both.

Whichever explanation is correct, the patterns of covariation indicate that, even at this anatomically crude level, brain structure evolution involved a complex set of relationships among individual structures. The chain of structures along the main axis in Fig. 3 (medulla–mesencephalon–diencephalon–neocortex) corresponds to a basic anatomical sequence from posterior (medulla) to anterior (neocortex) parts of the brain, and major projections are found between each of the links in this chain[10]. For example, the main part of the diencephalon, the thalamus, is the site of many major relays to and from the neocortex. The only difference between the patterns for the two orders is that cerebellum size correlates with neocortex size in primates, and with diencephalon size in insectivores. Extensive connections exist between neocortex and cerebellum. Given that many of these are relayed through the diencephalic thalamus,

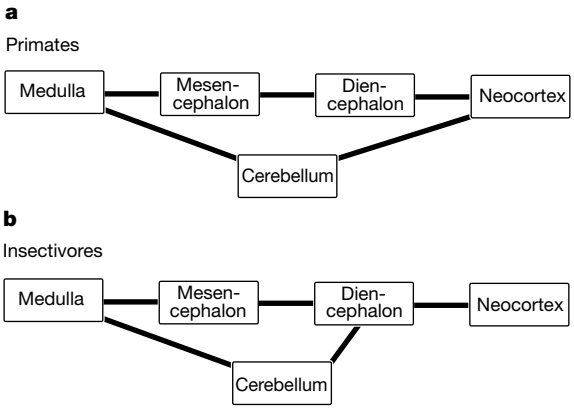

Figure 3 Correlated evolution among major brain structures. **a**, Primates. **b**, Insectivores. Connecting lines indicate significant positive partial correlations between the structures, from the analyses in Table 2. Hence, structures connected by such lines have evolved together independently of evolutionary change in the other structures.

there is likely to be a tight three-way evolutionary relationship amongst neocortex, cerebellum and diencephalon. This idea is supported by repeating the two analyses for the cerebellum with its primary correlate (either neocortex size or diencephalon size) removed. As predicted, cerebellum size in insectivores correlates significantly with neocortex size when diencephalon size is excluded ($P < 0.0001$), and in primates cerebellum size correlates significantly with diencephalon size when neocortex size is excluded ($P = 0.003$).

The major brain sub-divisions in Fig. 3 are anatomically and functionally heterogenous, and analysis of smaller, more functionally homogenous sub-divisions might reveal more fine-grained patterns of correlated evolution. We therefore tested for correlated evolutionary change in the individual components of specific functional units or systems. Data are available for six different systems, five in each order, yielding ten separate tests in all. The results (Fig. 4) reveal that, in all ten cases, components of functional systems evolved together independently of evolutionary size change in the other structures and in the rest of the brain. Hence, components of functional systems have highly specific evolutionary relationships, not attributable to their membership of more global systems such as the whole brain or the limbic system. In addition, although six of the tests also reveal a significant correlation with one of the other structures, in nine out of the ten cases the predicted relationship is the strongest (the only exception being where a structure—the insectivore hippocampus—correlates more strongly with the rest of the brain, perhaps reflecting the many diverse outputs and inputs of the hippocampus). Furthermore, some additional relationships are of course predicted by the hypothesis that functionally linked structures evolved together. Only two significant relationships out of the 48 tested seem anomalous in neurobiological terms, and these two can be reduced to a single case, as they involve the same two systems (amygdala and vestibular–cerebellar system in primates). The other significant results are explicable in functional terms. In both primates and insectivores there is a correlation between amygdala and olfactory components, reflecting the close anatomical and functional links between these structures[10–12]. In primates, the negative correlation between the lateral geniculate nucleus, a visual structure, and the olfactory bulb, may indicate a trade-off between visual and olfactory sensory modalities, perhaps associated with divergence into nocturnal versus diurnal niches[13]. The most striking feature of Fig. 4, however, is the combination of highly significant relationships within functional systems and the general absence of such relationships between systems.

These comparative analyses show that mammalian brain evolution involved size changes concentrated in specific structures and functional systems. One implication is that, as in birds[14], the cognitive and ecological significance of species differences in brain size should be evaluated by examining which neural systems in particular have been the target of selection. Although there may be some constraints on evolutionary change in individual neural

a Primates

	Rest of brain	1. Olfactory bulb	2. Entorhinal cortex	3. CBL of amygdala	4. Cerebellar nuclei	5. Visual cortex
1. Olfactory cortex	0.18 0.74	**0.31 3.43****	**0.09 0.67**	**0.32 2.13***	**0.23 1.11**	---
2. Hippocampus	0.37 1.46	**-0.06 -0.62**	**0.61 4.23*****	**-0.12 -0.77**	**0.14 0.66**	---
3. CM of amygdala	-0.36 -1.15	**0.12 1.04**	**-0.30 -1.71**	**0.91 4.96******	**0.65 2.57***	---
4. Vestibular nuclei	-0.38 -1.40	**0.13 1.28**	**-0.11 -0.69**	**0.35 2.16***	**0.95 4.27******	---
5. Lateral geniculate	1.04 1.49	**-0.52 -2.1***	**0.49 1.27**	**-0.40 -1.05**	**-0.70 -1.33**	**0.83 2.33***

b Insectivores

	Rest of brain	1. Olfactory bulb	2. Entorhinal cortex	3. CBL amygdala	4. Cerebellar nuclei	5. Superior olive
1. Olfactory cortex	-0.05 -0.59	**0.85 10.72******	**0.18 1.87**	**0.05 0.42**	---	---
2. Hippocampus	0.68 4.70******	**0.12 0.90**	**0.34 2.22***	**-0.12 -0.61**	---	---
3. CM amygdala	0.16 1.30	**0.28 2.46***	**0.01 0.10**	**0.54 3.19****	---	---
4. Vestibular nuclei	1.41 0.18	**-0.07 -0.33**	**0.25 0.85**	**0.04 0.14**	**0.65 2.36***	---
5. Cochlear nuclei	0.11 0.48	**0.07 0.51**	**-0.27 -1.36**	**-0.05 0.24**	---	**1.03 10.37******

Figure 4 Correlated volumetric evolution of functionally related brain structures. Each row summarizes results of one multiple regression based on independent contrasts. Contrasts in the volume of each structure in the left column were regressed on volumes of structures in the top row. In each cell: top figure, standardized regression coefficient; bottom figure, *t*-value; asterisks, level of significance, as in Table 2. A significant result means that the two structures evolved together independently of evolutionary change in the other structures for which results are reported in the same row. Predicted relationships are indicated by the bold boxes. These are the relationships between pairs of structures that are components within a functional system. The systems are 1, olfactory system; 2, hippocampal formation; 3, amygdala; 4, sensory-motor (vestibular) system; 5, visual system (primates) or auditory system (insectivores). CM, centro medial complex; CBL, cortico-basolateral complex; entorhinal cortex includes subiculum.

systems, tending to result in coordinated evolution among the majority of brain structures[3,7], such constraints are evidently insufficiently tight to prevent the type of system-specific change documented here. We conclude that mosaic evolution has been an important factor in the adaptive radiation of the mammalian brain. □

Methods

All volumetric measurements were made by the same research group using uniform methods[15–19]. Scaling relationships among biological variables are generally well described by the power function:

$$Y = kX^{\alpha} \quad (1)$$

$$\log Y = \alpha(\log X) + \log k \quad (2)$$

where Y and X are the variables, α and k are the parameters of the power equation. With logarithmic transformation the relationship becomes linear, so that the exponent is expressed as the slope of the line:

Slopes were determined using least-squares regression. As coefficients of determination in all scaling analyses were uniformly high (>0.92), use of alternative line-fitting techniques would have minimal impact. To show the presence of taxonomic grade shifts clearly, we based graphs on values for individual species, rather than on independent contrasts (see below). A grade shift is defined as a taxonomic difference in the mean value of a continuous variable after the effects of scaling have been taken into account.

To verify statistically the existence of significant grade shifts among taxa, we used a procedure based on the method of independent contrasts[20–22]. This procedure involves (1) demonstration that the slopes for the different taxa are homogenous, based on a t-test on the residuals from a regression of independent contrasts for the dependent variable on contrasts for the scaling variable; (2) demonstration that the contrast between the taxa being compared is an outlier, and hence has an unusually large residual value compared with other contrasts in the data set[22]. The program and procedures for generating independent contrasts have been described[22], and the phylogenies of primates and insectivores are from ref. 23 and R. Grenyer (personal communication), respectively.

Independent contrasts were also used to test for correlated evolution among brain structures. Assumptions of the method were checked as described in ref. 22. In these analyses, data for strepsirhine and haplorhine primates were pooled to yield adequate sample size. In the analyses presented in Table 2 (summarized in Fig. 3), independent contrasts in the volume of each structure were tested against the other structures in separate multiple regressions. This is equivalent to testing for significant partial correlations amongst the five structures, with the advantage that the regressions can be set through the origin as required with independent contrasts. A similar procedure was used in the analyses of correlated evolution among sub-components of functional systems (Fig. 4). We made predictions about which specific structures were likely to have evolved together, on the basis of well-known neurobiological links, and tested for correlated evolution between them, controlling for variation in the rest of the brain. We tested such predictions for pairs of structures within six systems, the olfactory system (olfactory cortex and olfactory bulb), visual system (primary visual cortex and lateral geniculate nucleus), auditory system (cochlear nuclei and superior olive), a sensory–motor (vestibular) system (vestibular nuclei of the medulla and cerebellar nuclei), the hippocampal formation (hippocampus and entorhinal cortex plus subiculum) and the amygdala (cortico-basolateral and centro-medial amygdala). These were chosen because of the close and relatively uncontroversial anatomical and functional links between the structures within each system, and because of the availability of comparative volumetric data. To assess how specific the relationships among components of each functional system were, we included components of the other systems as independent variables in the multiple regressions. However, because relatively few data were available for the primate visual system, the insectivore auditory system and insectivore vestibular system, components of these were excluded as independent variables in the analyses of other systems. In each case, variation in the volume of the other structures was taken into account using multiple regression. Olfactory cortex volume in primates was estimated as palaeocortex minus amygdala, thus including the lateral olfactory tract, olfactory tubercle and fibres of passage[15,16].

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The temporal response of the brain after eating revealed by functional MRI

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After eating, the human brain senses a biochemical change and then signals satiation, but precisely when this occurs is unknown. Even for well-established physiological systems like glucose–insulin regulation, the timing of interaction between hormonal processes and neural events is inferred mostly from blood sampling[1–6]. Recently, neuroimaging studies have provided *in vivo* information about the neuroanatomical correlates of the regulation of energy intake[7–10]. Temporal orchestration of such systems, however, is crucial to the integration of neuronal and hormonal signals that control eating behaviour[11]. The challenge of this functional magnetic resonance imaging study is to map not only where but also when the brain will respond after food ingestion. Here we use a temporal clustering analysis technique to demonstrate that eating-related neural activity peaks at two different times with distinct localization. Importantly, the differentiated responses are interacting with an internal signal, the plasma insulin. These results support the concept of temporal parcellation of brain activity[12], which reflects the different natures of stimuli and responses. Moreover, this study provides a neuroimaging basis for detecting dynamic processes without prior knowledge of their timing, such as the acute effects of medication and nutrition in the brain.

The timing for the regulation of food ingestion is different from that for the control of sensorimotor or cognitive tasks. The question addressed here is: using functional magnetic resonance imaging