Evolution of the cortico-cerebellar complex in primates.

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Abstract

Investigations into the evolution of the primate brain have generally neglected the role of connectivity in determining which brain structures have changed in size, focussing instead on changes in the size of the whole brain or of individual brain structures, such as the neocortex, in isolation. We show that the primate neocortex, cerebellum and vestibular nuclei exhibit correlated volumetric evolution. At a relatively fine-grained level of resolution, the evolutionary correlations correspond to known patterns of connectivity among these structures (amongst specific nuclei, for example). These results support the idea that brains evolved by mosaic size change in arrays of connected structures. Furthermore, they suggest that the much discussed expansion of the primate neocortex should be re-evaluated in the light of conjoint cerebellar expansion.

Introduction

Compared to other mammals of similar body size, primates have evolved an unusually large brain[1,2]. This large size is not thought to be due to the production of new structures, but due to the modification of existing ones[3-5]. Hence, the brains of primates and other mammals are similar in terms of the types of structures which they contain. Where they differ is in the precise form, arrangement and relative size of these structures. Differences can vary from simple changes in size to more complex reorganization of neurons and their connections. However, research on brain evolution has focussed primarily on simple size changes in overall brain size or individual brain structures, particularly the neocortex (refs). While such research is certainly justified, it is limited by the fact that brain structures do not function in isolation, but rather as parts of distributed systems (refs).

Brain systems are groups of brain structures which are intimately connected and which cooperate to effectively process a particular type of information. The format of systems is such that the expertise of each of the different brain structures involved is exploited for a particular function of that system of which it forms a part: these are functional systems with a division of labour. The brain contains large numbers of such brain systems and these often work in parallel, thereby increasing the efficiency of the brain.

Investigations into the evolution of the primate brain should take account of these systems by looking at interconnected structures rather than focussing solely on individual brain regions. At present, there is much controversy over whether the brain evolves as a coordinated whole[6] or whether individual structures or systems can evolve independently of changes in other parts of the brain (mosaic evolution)[7]. This paper tests the mosaic change hypothesis by analysing patterns of correlated evolution among interconnected structures. Given that functional systems are distributed across multiple structures, it is predicted that individual structures will be found to show correlated changes with other structures involved in the same functional system independently of structures involved in different systems. One important point to note here is the fact that brain structures may, and often do, participate in more than one functional system (most notably the neocortex which is involved in numerous different systems). This means that changes in the size of one structure may be related to a large number of functional systems, not just one. For this reason, it is necessary to look at sub-parts of brain structures, to look at small-scale changes in the particular areas included in the system of interest. In this way, it should be possible to gain a more precise understanding of what a change in the size of a brain structure actually means, that is to say, to discover precisely which system this change reflects.

In this paper we focus on inter-relationships among the cerebellum, neocortex, the relays between them (pons and thalamus) and the vestibular system. Despite the fact that the cerebellar cortex has a simple and uniform structure, its function is highly heterogeneous. It has been implicated in the planning, execution and control of motor actions as well as, more controversially, in a number of cognitive functions[8-10]. Cerebellar systems are of interest because recent evidence suggests that they have expanded in some groups of primates[11]. In addition, there is evidence for conjoint expansion of the cerebellum with an area that has been the subject of intense scrutiny, the neocortex[7]. Finally, volumetric comparative data are available on individual cerebellar and vestibular nuclei[12].

The cerebellar systems

The cerebellum receives input from the neocortex (via the pons), the vestibular system (lateral vestibular nucleus) and the spinal cord. The output structures of the cerebellum are the cerebellar nuclei, which send projections to the neocortex (motor, premotor and prefrontal areas) via the ventrolateral nucleus of the thalamus. The cerebellar nuclei also send projections to the spinal cord via the lateral vestibular nucleus, the red nucleus or the brain stem reticular formation.

The current paper aims to investigate correlated evolution among these structures. Unfortunately, data are not currently available on the volumes of the red nucleus, the reticular formation or particular regions of the spinal cord and it will therefore not be possible to include these structures in the current analyses. Data are, however, available on the volume of the individual structures involved in both the cerebellar-vestibular system and the cerebellar-neocortical system and these two important brain systems will be the focus of the current investigation. The principal connections involved in these cerebellar systems are illustrated in Figure 1 below.

----------------FIGURE 1 HERE-----------------

The investigation is split into the following three parts:

(i) The neocortex and the cerebellum

The first part expands on studies showing that the cerebellum has undergone correlated evolutionary size changes with the neocortex[7,13,14]. The evolution of the cerebellum and the neocortex is investigated in more detail here to determine which particular areas of the cerebellum have shown correlated evolutionary changes with the neocortex. Data are currently available for the volume of the cerebellum as a whole and for the volume of the cerebellar nuclei, and these are used to calculate the volume of the non-nuclear cerebellum (which includes the cerebellar cortex, the major input area of the cerebellum). It is crucial that in these analyses, variation in the size of other brain structures is partialled out. This means that any significant relationships found between cerebellar and neocortical evolution are independent of evolutionary changes in other structures, hence specific to the cortico-cerbellar structures under investigation..

(ii) The pons and the thalamus

In the second part, the pons and the thalamus are analysed. This is important because there are no direct neural connections between the neocortex and the cerebellum. Projections from the neocortex to the cerebellum pass through the pons, and projections from the cerebellum back to the neocortex pass through the thalamus.

(iii) The vestibular system

The final part looks at the other projections to and from the cerebellum. As can be seen in Figure 1, in addition to the neocortical circuit, the cerebellum also receives information from, and sends information to, the vestibular system. It is the lateral vestibular nucleus in particular that has connections to the cerebellum. This nucleus projects to the flocculonodular lobe of the cerebellum. Outputs back to the lateral vestibular nucleus come from the middle cerebellar nucleus (MCN). Unfortunately, data are currently lacking on the volumes of the ventrolateral nucleus of the thalamus and on the flocculonodular lobe of the cerebellum. The volume of the whole thalamus and the volume of the non-nuclear cerebellum, respectively, are therefore used as the best currently possible approximations.

Methods

We used the method of independent contrasts, which enables the assessment of correlated evolution in comparative data sets (refs). The method works by calculating standardised contrasts between sister taxa in the phylogeny. Hence, a contrast score represents the evolutionary change that has occurred since the common ancestor of the sister taxa. These contrasts can then be subjected to standard methods of correlation and regression. The particular computer package used in the current analyses is C.A.I.C. (Comparative analysis by independent contrasts)[15] which uses Felsenstein's method of independent comparisons.

As we were interested in whether particular components of cerebellum, neocortex and vestibular system evolved together independently of variation in other brain structures, we also calculated contrasts for the rest of the brain (whole brain size-(cerebellum+neocortex+vestibular nuclei)), and then partialled out the effects of this variable using regression. This was done by regressing contrasts in, for example, the cerebellum, on contrasts in the rest of the brain, and taking residuals. These residuals are referred to as relative contrasts in cerebellum size.

Data on the volume of the cerebellum (including individual cerebellar nuclei), the neocortex, the vestibular system (including the individual vestibular nuclei) and the thalamus for up to 44 species of primates comes from Stephan[16]. Data on the volume of the pons comes from Matano et al.[17]. The original estimates of cerebellar volume incorporated the pons (Matano et al. 1985), so we obtained cerebellum volumes by subtracting the volume of the pons from these estimates. Data on the volume of the cerebellum and the whole brain in *Pan paniscus* and *Pongo pigmaeus* (which was not included in the Stephan et al. data set) come from Semendeferi and Damasio[18] and measurements of the volume of the neocortex in these species comes from Rilling and Insel[19]. Volumes of the cerebellar nuclei are obtained from Matano and Hirasaki[12] and volumes of the non-nuclear cerebellum are calculated by subtracting the volumes of the nuclei from whole cerebellum volume. "Rest of the brain" volumes are calculated by subtracting the relevant brain structures from whole brain volumes for the various different calculations. All data were analysed in logarithmic form making them suitable for independent contrasts analysis[15]. A total of 44 species of primate were included.

Results

In each case the significance level is set at $p<0.05$. The graphs are provided only for those correlations which are significant.

(i) The neocortex and the cerebellum

Correlations between relative contrasts in neocortex size and relative contrasts in cerebellum size are presented in Table 1.

Graphs (i), (ii) and (iii) show the significant evolutionary relations for this data set. All three of the comparisons between the neocortex and the cerebellum were found to be significant. The most significant relationships were between the neocortex and the whole cerebellum ($r^2=0.29$, $p=0.0003$) and the non-nuclear cerebellum alone ($r^2=0.28$, $p=0.0003$,). A weaker though still significant positive correlation was found between the neocortex and the cerebellar nuclei ($r^2=0.20$, $p=0.003$).

(ii) The pons and the thalamus

Relative contrasts in pons size and thalamus size show varying correlations with relative contrasts in cerbellum and neocortex size (Table 2).

The pons and the neocortex have shown significantly and positively correlated volumetric changes over evolutionary time (r^2=0.15, p=0.01,). A slightly weaker but still significant correlation is found between the cerebellum and the pons (r^2=0.10. p=0.04). However, the pons correlates only with the non-nuclear part of the cerebellum (r^2=0.09, p=0.05), and not with the cerebellar nuclei (r^2=0.06, p=0.14). Conversely, the thalamus correlates positively and highly significantly with the cerebellar nuclei (r^2=0.54, p<0.0001), but not with the non-nuclear part of the cerebellum (r^2=0.14, p=0.07). These findings accord with the anatomical connections, since the pons projects directly to the cerebellar cortex, whilst the thalamus receives direct projections from the cerebellar nuclei (Figure 1).

(iii) The vestibular system

Relative contrasts in vestibular system size and lateral vestibular nucleus size show varying correlations with relative contrasts in cerebellum and neocortex size (Table 3). Relative vestibular nucleus volumes are uncorrelated with relative volume of both the whole cerebellum and of the non-nuclear part of the cerebellum. There is, however, a strong positive correlation between vestibular and cerebellar nuclei. As predicted by anatomical connections, this correlation is strongest for the medial cerebellar nucleus (r^2=0.48, compared with 0.33 and 0.17 for the other two cerebellar nuclei). When the lateral vestibular nucleus is regressed on each of the three cerebellar nuclei using multiple regression, only the medial cerebellar nucleus shows a significant relationship (MCN, t=3.99, p=0.0003; ICN, t=0.57, p=-0.57; LCN, t=-0.50, p=0.62). Similarly another multiple regression indicates that, of the vestibular nuclei, it is the lateral nucleus which shows the closest relationship with the medial cerebellar nucleus (LVN, t=3.87, p=0.0005; SVN, t=-0.34, p=0.73; MVN, t=2.11, p=0.04; DVN, t=1.36, p=0.18). Hence, patterns of correlated evolution reflect the strong anatomical relationship between medial cerebellar and lateral vestibular nuclei.

--------------TABLES 1,2 and 3 HERE----------------

-----------------FIGURE 2 HERE-------------------

Discussion

These results corroborate the suggestion that, during the radiation of the primate order, the neocortex and cerebellum have undergone correlated evolution (Barton & Harvey 2000). They additionally show that other related structures, the pons, thalamus and vestibular complex, have also changed in concert. Furthemore, we have shown that, at a finer scale, the patterns of correlated evolution are to a great extent predictable from information on anatomical connectivity. Hence these findings lend further weight to the idea that the primate brain has evolved as a functional mosaic. The functional systems involved are distributed across major brain regions, including the brainstem, midbrain and forebrain, emphasizing the need for comparative studies to go beyond the analysis of individual brain structures and to focus instead on distributed systems. Whilst the limitations of the available data dictate that our analyses are still crude in terms of defining functional systems, it is encouraging that such predictions as could be made were supported. In the future it would be useful to see further refinement of hypotheses and tests using data on, for example, individual thalamic nuclei (but see Barton 1998), and regions of the cerebellar cortex.

The neocortex projects, via the pons, directly to the cerebellar cortex, but not to cerebellar nuclei. In accord with this, the neocortex and pons correlated more strongly with cerebellar cortex than with the cerebellar nuclei. The cerebellar nuclei, on the other hand, were found to correlate strongly with the thalamus, the structure to which they project. For the cerebellar-vestibular system, correlated evolution was found at the level of individual cerebellar nuclei. In these analyses, the two nuclei with direct connections, the lateral vestibular nucleus and medial cerebellar nucleus, exhibited strongly correlated evolution even after controlling for variation in the size of the other nuclei.

Although the thalamus and neocortex are extensively connected, there was only a weak correlation between these two structures (p=0.06). Possible explanations include the fact that there was a reduced sample size for thalamus volume and the fact that data were not available for the particular area of the thalamus which is involved in the cerebellar-neocortical system (the ventrolateral thalamic nucleus).

A mechanism by which the coordinated evolution of cortico-cerebellar elements might have occurred, was proposed by Matano & Hirasaki[12]. They suggested that a decrease in the size of a nucleus reflects either a decrease in the number of neurons that it contains, or a decrease in the size of the arborization of dendrites and thus a decrease in the number of synaptic terminals. Therefore, a decrease in the size of one area might indicate that there are simply not enough neurons for the number of synaptic connections that existed before, or that the level of dendritic arborization is not high enough to support the same level of connectivity. Either way, a decrease in the size of a cerebellar nucleus will result in a decrease in the connections of that nucleus. Conversely, an increase in size would either reflect an increase in the number of neurons, or an increase in the number of synaptic terminals available for forming new connections, thus increasing the number of projections. This clearly shows that changes in the size of a brain structure affect the connections of that structure and consequently also the areas to which it is connected.

Conclusions and summary

Previous work on the evolution of the primate brain has generally focussed on changes in individual structures. Brain structures, however, do not function in isolation, but contribute to distributed functional systems. The present analyses demonstrate correlated evolution among neocortex, cerebellum, vestibular complex and relay stations (pons and thalamus). At as fine a scale as allowed by the available data, the patterns of correlated evolution reflect functional connectivity. Finally, our results suggest that the focus on the neocortex as the principle area of change in primate brain evolution (references: Barton & Dunbar & others) may have been excessive, and that some attention should now be paid to cortico-cerbellar circuits and the cognitive functions they mediate. These might include…

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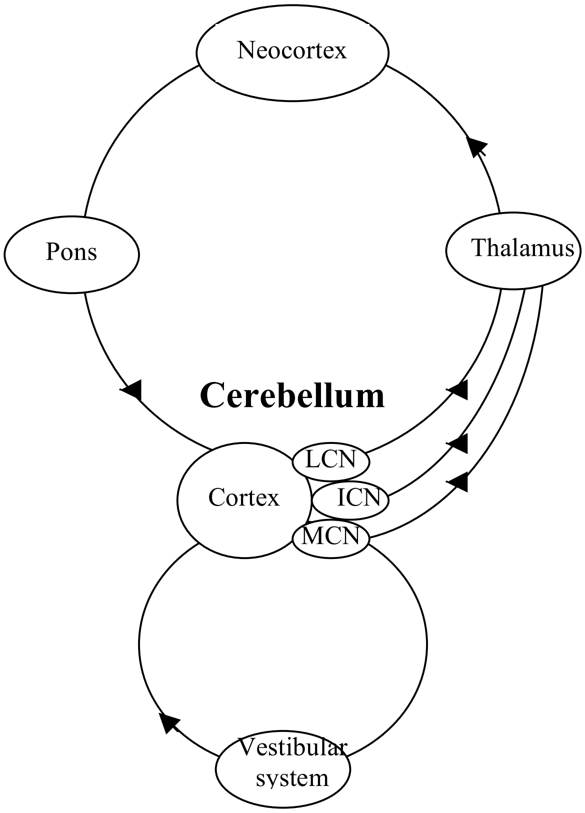
Figure 1: The major connections of the cerebellum.

Add: there are also projections to the reticular formation and the red nucleus, however sufficient volumes for these structures are not yet available for primates and it is therefore not yet possible to include these structures in our analyses.



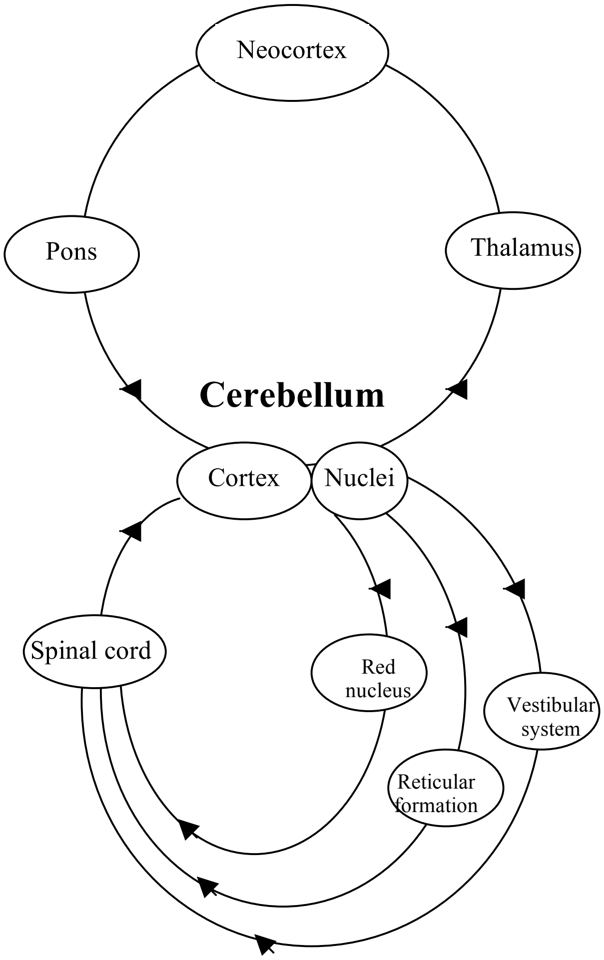
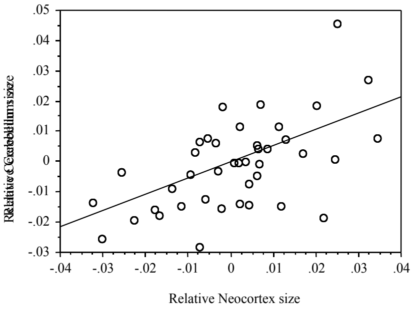
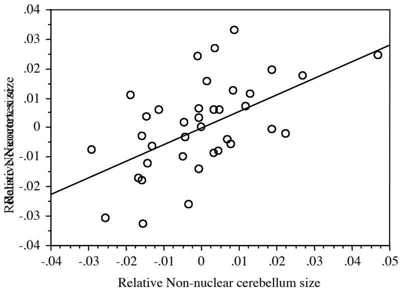

Neocortex
Pons
Thalamus
Cerebellum
Cortex
Nuclei
Spinal cord
Red nucleus
Vestibular system
Reticular formation

Figure 2. **Regression plots after independent contrast analysis to show the correlated evolution of pairs of brain structures involved in cerebellar systems.**

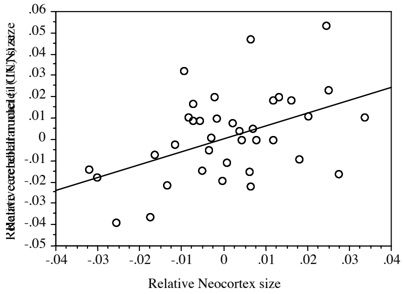
(i) The whole cerebellum and the neocortex



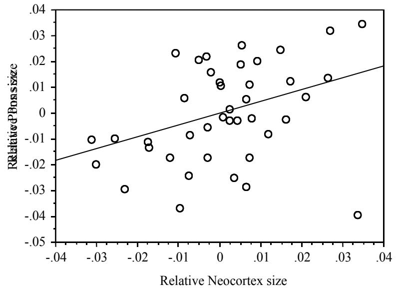
(ii) The non-nuclear cerebellum and the neocortex



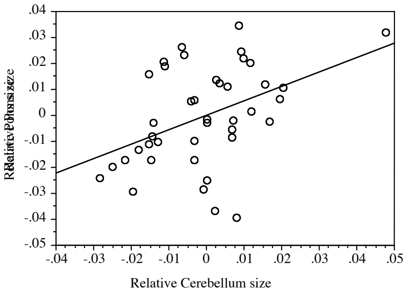
(iii) The cerebellar nuclei and the neocortex



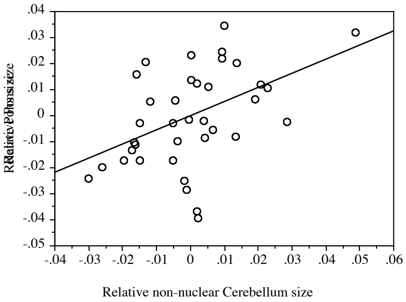
(iv) The neocortex and the pons



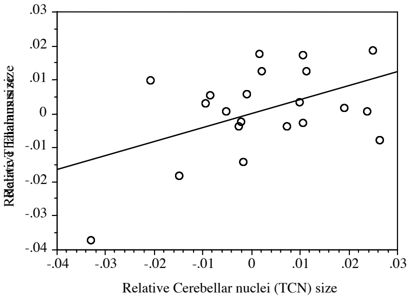
(v) The whole cerebellum and the pons



(vi) The non-nuclear cerebellum and the pons



(vii) The cerebellar nuclei and the thalamus



(viii) The middle cerebellar nucleus (MCN) and the lateral vestibular nucleus

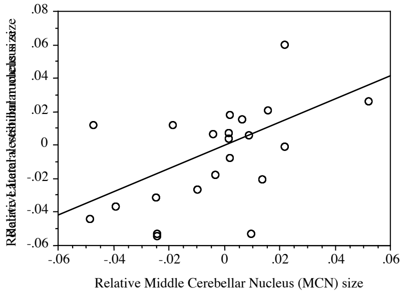


Table 1. Correlated volumetric evolution of the neocortex and cerebellar areas as revealed by bivariate regressions on residuals of independent contrasts.

	Whole Cerebellum		Non-nuclear cerebellum		Cerebellar nuclei	
Neocortex	**p**	0.0003	**p**	0.0003	**p**	0.0033
	f	16.23	**f**	15.38	**f**	9.82
	r^2	0.29	**r^2**	0.28	**r^2**	0.20
	d.f.	1, 40	**d.f.**	1, 40	**d.f.**	1, 40

Table 2. Correlated volumetric evolution among brain structures involved in the cerebellar-neocortical system as revealed by bivariate regressions on residuals of independent contrasts.

	Neocortex		Whole Cerebellum		Non-nuclear cerebellum		Cerebellar nuclei	
Pons	**p**	0.013	**p**	0.04	**p**	0.05	**p**	0.14
	f	6.86	**f**	3.99	**f**	3.91	**f**	2.29
	r^2	0.15	**r^2**	0.10	**r^2**	0.09	**r^2**	0.06
	d.f.	1, 39	**d.f.**	1, 39	**d.f.**	1, 39	**d.f.**	1, 39
Thalamus	**p**	0.06	**p**	0.06	**p**	0.07	**p**	<0.0001
	f	3.90	**f**	4.01	**f**	3.63	**f**	25.49
	r^2	0.15	**r^2**	0.15	**r^2**	0.14	**r^2**	0.54
	d.f.	1, 22	**d.f.**	1, 22	**d.f.**	1, 22	**d.f.**	1, 22

Table 3: **Correlated volumetric evolution among brain structures involved in the cerebellar-vestibular system as revealed by bivariate regressions on residuals of independent contrasts.**

	Whole Cerebellum		Non-nuclear cerebellum		Cerebellar nuclei		MCN	
Vestibular System	**p**	0.75	**p**	0.85	**p**	<0.0001	**p**	<0.0001
	f	0.10	**f**	0.037	**f**	21.84	**f**	35.00
	r^2	0.003	**r^2**	0.001	**r^2**	0.37	**r^2**	0.48
	d.f.	1, 38	**d.f.**	1, 38	**d.f.**	1, 38	**d.f.**	1, 38
Lateral vestibular nucleus	**p**	0.75	**p**	0.86	**p**	0.0002	**p**	<0.0001
	f	0.32	**f**	0.03	**f**	16.49	**f**	35.18
	r^2	0.003	**r^2**	0.001	**r^2**	0.30	**r^2**	0.48
	d.f.	1, 38	**d.f.**	1, 38	**d.f.**	1, 38	**d.f.**	1, 38

P values, f values, regression coefficients (r^2) and degrees of freedom (d.f.) are given for each correlation. Significant f values indicate that the two structures in question have shown highly correlated change over evolution after the effects of evolutionary change in the rest of the brain has been removed.