Brain structures and life-span in primate species

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ABSTRACT   In haplorhine primates, when the effect of body weight is removed, brain weight is correlated with maximum recorded life-span. In this paper we have analyzed the relationships between volumes of specific brain structures and life-span. When the effect of body weight is removed, the volumes of many brain structures are significantly, positively correlated with maximum recorded life-span. However, the volumes of the medulla and most first-order sensory structures do not correlate with life-span. The cerebellum is the brain structure that best correlates with life-span. Parts of the cerebellum are particularly vulnerable to age-related loss of mass in humans. For another measure of the life cycle, female reproductive age, a similar set of brain structures is significantly, positively correlated (again with the exceptions of the medulla and most first-order sensory structures). There are some differences between the structures correlated for life-span and female reproductive age. For example, the hippocampus and lateral geniculate nucleus correlate with female reproductive age but do not correlate with life-span. In strepsirhine primates, when the effect of body weight is removed, total brain weight does not significantly correlate with either life-span or female reproductive age. However, the volumes of some brain structures in strepsirhines do correlate with these life-cycle parameters. The centromedial complex of the amygdala is the only structure to correlate with life-span in both strepsirhine and haplorhine primates. This structure participates in the regulation of blood pressure and in the stress response, which may be key factors governing life-span.

In a previous study (1), we found in haplorhine primate species (tarsiers, monkeys, apes, and humans) that brain weight is correlated with maximum recorded life-span and female average age of first reproduction when the effect of body size is removed. In strepsirhine primates (lorises and lemurs) there is no statistically significant correlation between brain weight and either life-span or female reproductive age. The purpose of this paper is to examine the relationships between the volumes of specific brain structures and both life-span and female reproductive age.

MATERIALS AND METHODS

We used maximum recorded life-span because it should measure under ideal circumstances the genetic potential for longevity for each species. To find the maximum recorded life-spans, we obtained data from 138 zoos and research institutions throughout the world. We used the same life-span data as in our previous paper (1); due to space limitations, we shall publish the life-span records separately. The maximum recorded human life-span was obtained from MacFarlan (2).

Volumes of brain structures were obtained from the quantitative studies of Stephan and his coworkers (3–13). We used data on female average age at first reproduction from a published list compiled by Ross (14). Data on diet were

obtained from the book *Primate Societies* (15). We used SYSTAT 5.2 to assist us in the statistical analysis.

As in the previous paper (1), we removed the effect of body weight by plotting the base 10 logarithm of the parameter in question (such as brain-structure volume or life-span) against the base 10 logarithm of body weight. The distance in the *y* dimension between the regression line and each data point was added to 1, giving a value >1 for points that fall above the line and <1 for points that fall below the line. This value is the *residual* value for each species. The addition to 1 was used to make all residual values positive. We used the least-squares regression as the basis for calculating brain and life-span residuals because this procedure removes the effect of body size plotted along the *x* axis (16). We have sought to determine to what degree these residuals for primate species are correlated, using a Pearson correlation. In the following discussion, *n* is the sample size, *r* is the Pearson correlation coefficient, and *P* is the probability associated with the χ^2 test of the significance of the correlation. Because the human brain-structure volumes and life-span are much greater than those of the other haplorhines, we have calculated the *r* and *P* values with and without the human in the haplorhine data set. In Table 1 the *n*, *r*, and *P* values calculated without the human are enclosed in parentheses.

RESULTS

Brain Structures and Life-Span in Haplorhines. Correlations between the residuals for various parameters and the residuals for maximum life-span and average female age at first reproduction in haplorhine primates are presented in Table 1. When the effect of body weight is removed, many brain structures are significantly, positively correlated with life-span with the conspicuous exceptions of the medulla and most first-order sensory structures, such as the main and accessory olfactory bulbs, the lateral geniculate nucleus, and the vestibular nuclei. Plots of cerebellum, neocortex, amygdala, and hypothalamus residuals relative to life-span in haplorhine primates are illustrated in Fig. 1. One structure, the subcommissural organ, is significantly negatively correlated with life-span in haplorhines. So little is known about this ependymal structure that we cannot offer any interpretation for its negative correlation with life-span (18).

Brain Structures and Reproductive Age in Haplorhines. With respect to female reproductive age in haplorhines, a similar set of brain structures are significantly, positively correlated, generally with lower *r* values than for life-span. As with life-span, the notable exceptions are the medulla and most first-order sensory structures, which are not correlated. There are, however, some important differences between the structures correlated with life-span and those correlated with female reproductive age. Neocortical gray matter and the centromedial complex of the amygdala correlate with life-span but do not correlate with female reproductive age. The lack of correlation between neocortical gray matter and female reproductive age may have resulted from small sample size because in a larger sample for neocortex (gray plus associated white matter), female reproductive age is significantly correlated, although it correlates much less than with

Table 1. Life-span and female age at first reproduction residuals vs. residuals for volumes of various brain structures in haplorhine primates

Residual*	Versus life-span residual			Versus female age at first reproduction residual		
	n	r	P	n	r	P
Whole brain	26	**0.672**	<0.001	23	**0.514**	0.012
	(25)	**(0.541)**	(0.005)	(22)	**(0.491)**	(0.020)
Female age at first reproduction	46	**0.429**	0.003			
	(45)	**(0.409)**	(0.005)			
Amygdala, whole	23	**0.623**	0.001	21	**0.481**	0.027
	(22)	**(0.473)**	(0.026)	(20)	**(0.459)**	(0.042)
Amygdala, centromedial complex	24	**0.522**	0.009	22	0.311	0.159
	(23)	(0.307)	(0.154)	(21)	(0.243)	(0.288)
Amygdala, corticobasolateral complex	24	**0.643**	0.001	22	**0.508**	0.016
	(23)	**(0.513)**	(0.012)	(21)	**(0.485)**	(0.026)
Amygdala, magnocellular part of basal nucleus	24	**0.453**	0.026	22	**0.553**	0.008
	(23)	**(0.447)**	(0.032)	(21)	**(0.539)**	(0.012)
Anterior commissure	26	0.186	0.363	23	0.163	0.459
	(25)	(0.083)	(0.695)	(22)	(0.123)	(0.584)
Cerebellar nuclei, interpositus	25	−0.051	0.810	22	0.042	0.853
	(24)	(0.043)	(0.841)	(21)	(0.081)	(0.728)
Cerebellar nuclei, lateral	25	**0.513**	0.009	22	**0.470**	0.027
	(24)	**(0.425)**	(0.039)	(21)	**(0.435)**	(0.049)
Cerebellar nuclei, medial	25	−0.042	0.843	22	−0.143	0.526
	(24)	(−0.058)	(0.788)	(21)	(−0.147)	(0.525)
Cerebellar nuclei, total	25	0.299	0.146	22	0.257	0.248
	(24)	(0.242)	(0.255)	(21)	(0.226)	(0.324)
Cerebellum, whole	26	**0.750**	<0.001	23	**0.512**	0.012
	(25)	**(0.638)**	(0.001)	(22)	**(0.501)**	(0.017)
Diencephalon	26	**0.561**	0.003	23	**0.553**	0.006
	(25)	**(0.502)**	(0.011)	(22)	**(0.527)**	(0.012)
Globus pallidus	15	0.507	0.054	14	0.445	0.110
	(14)	(0.505)	(0.066)	(13)	(0.427)	(0.146)
Hippocampus	26	0.257	0.205	23	**0.580**	0.004
	(25)	(0.006)	(0.979)	(22)	**(0.567)**	(0.006)
Hypothalamus	15	**0.595**	0.019	14	**0.540**	0.046
	(14)	(0.454)	(0.104)	(13)	(0.507)	(0.077)
Lateral geniculate nucleus	23	0.113	0.608	21	**0.503**	0.020
	(22)	(0.283)	(0.202)	(20)	**(0.557)**	(0.011)
Lateral olfactory tract	26	0.088	0.669	23	−0.029	0.894
	(25)	(0.008)	(0.970)	(22)	(0.063)	(0.782)
Medial habenular nucleus	20	−0.038	0.872	18	−0.217	0.388
	(19)	(−0.028)	(0.908)	(17)	(−0.227)	(0.382)
Medulla	26	0.223	0.274	23	0.313	0.146
	(25)	(0.152)	(0.469)	(22)	(0.284)	(0.200)
Mesencephalon	26	**0.565**	0.003	23	**0.466**	0.025
	(25)	**(0.439)**	(0.028)	(22)	**(0.429)**	(0.046)
Neocortex, including white matter	26	**0.621**	0.001	23	**0.477**	0.021
	(25)	**(0.509)**	(0.009)	(22)	**(0.441)**	(0.040)
Neocortex, gray matter	13	**0.611**	0.026	12	0.363	0.246
	(12)	(0.421)	(0.173)	(11)	(0.309)	(0.356)
Neocortex, lamina 1	13	**0.565**	0.044	12	0.332	0.292
	(12)	(0.335)	(0.288)	(11)	(0.270)	(0.422)
Neocortex, laminae 2–6	13	**0.615**	0.025	12	0.365	0.244
	(12)	(0.430)	(0.164)	(11)	(0.311)	(0.352)
Neocortex, white matter	13	0.529	0.063	12	0.238	0.457
	(12)	(0.457)	(0.136)	(11)	(0.190)	(0.577)
Nucleus of the lateral olfactory tract	5	−0.435	0.464	5	0.228	0.712
	(4)	(−0.435)	(0.468)	(4)	(0.228)	(0.715)
Olfactory bulb, accessory	12	0.109	0.735	11	0.155	0.649
	(11)	(0.109)	(0.735)	(10)	(0.155)	(0.650)
Olfactory bulb, main	26	−0.028	0.892	23	0.030	0.892
	(25)	(−0.079)	(0.709)	(22)	(0.014)	(0.949)
Olfactory tubercule	26	**0.434**	0.027	23	0.153	0.486
	(25)	(0.268)	(0.196)	(22)	(0.063)	(0.782)
Pineal	20	0.130	0.584	18	0.376	0.124
	(19)	(−0.042)	(0.864)	(17)	(0.299)	(0.244)

Table 1. Continued

Residual*	Versus life-span residual			Versus female age at first reproduction residual		
	n	r	P	n	r	P
Piriform lobe	26	**0.615**	0.001	23	**0.463**	0.026
	(25)	**(0.443)**	(0.027)	(22)	**(0.440)**	(0.041)
Prepiriform cortex	26	**0.500**	0.009	23	0.366	0.086
	(25)	(0.297)	(0.150)	(22)	(0.312)	(0.158)
Primary visual cortex gray matter	22	0.066	0.769	20	0.332	0.153
	(21)	(0.188)	(0.413)	(19)	(0.367)	(0.122)
Primary visual cortex gray matter, lamina 1	13	0.086	0.780	12	0.273	0.391
	(12)	(0.208)	(0.516)	(11)	(0.299)	(0.372)
Primary visual cortex gray matter, laminae 2–6	13	0.064	0.836	12	0.271	0.394
	(12)	(0.218)	(0.496)	(11)	(0.305)	(0.362)
Primary visual cortex, total	22	0.075	0.741	20	0.343	0.139
	(21)	(0.196)	(0.395)	(19)	(0.378)	(0.111)
Primary visual cortex, white matter	22	0.073	0.745	20	0.299	0.201
	(21)	(0.218)	(0.342)	(19)	(0.347)	(0.146)
Retrobulbar cortex	26	0.068	0.741	23	0.196	0.370
	(25)	(−0.273)	(0.188)	(22)	(0.109)	(0.628)
Septum	26	**0.576**	0.002	23	**0.414**	0.049
	(25)	(0.309)	(0.132)	(22)	(0.413)	(0.056)
Striatum	26	**0.535**	0.005	23	**0.517**	0.011
	(25)	**(0.507)**	(0.010)	(22)	**(0.494)**	(0.020)
Subcommissural body	20	**−0.460**	0.041	18	−0.252	0.314
	(19)	(0.236)	(0.330)	(17)	(0.074)	(0.777)
Subfornical body	20	−0.198	0.403	18	−0.334	0.176
	(19)	(0.105)	(0.669)	(17)	(−0.198)	(0.448)
Substantia innominata	26	**0.619**	0.001	23	**0.486**	0.019
	(25)	**(0.668)**	(<0.001)	(22)	**(0.478)**	(0.025)
Subthalamus	15	0.512	0.051	14	0.453	0.104
	(14)	(0.502)	(0.067)	(13)	(0.433)	(0.140)
Telencephalon	26	**0.645**	<0.001	23	**0.501**	0.015
	(25)	**(0.519)**	(0.008)	(22)	**(0.472)**	(0.027)
Thalamus	15	**0.610**	0.016	14	**0.600**	0.023
	(14)	(0.499)	(0.069)	(13)	**(0.573)**	(0.041)
Triangular nucleus of the septum	20	−0.414	0.069	18	−0.337	0.172
	(19)	(0.182)	(0.456)	(17)	(−0.143)	(0.584)
Trigeminal complex	26	**0.410**	0.038	23	**0.434**	0.038
	(25)	(0.251)	(0.227)	(22)	(0.393)	(0.071)
Ventral pons	25	**0.449**	0.024	22	0.296	0.181
	(24)	**(0.433)**	(0.035)	(21)	(0.273)	(0.231)
Vestibular complex, total	26	0.072	0.727	23	0.142	0.517
	(25)	(0.146)	(0.487)	(22)	(0.165)	(0.463)
Vestibular complex, inferior nucleus	26	−0.037	0.857	23	0.173	0.431
	(25)	(−0.007)	(0.973)	(22)	(0.185)	(0.411)
Vestibular complex, lateral nucleus	26	−0.124	0.545	23	−0.265	0.222
	(25)	(−0.056)	(0.789)	(22)	(−0.241)	(0.281)
Vestibular complex, medial nucleus	26	0.146	0.477	23	0.190	0.386
	(25)	(0.250)	(0.228)	(22)	(0.223)	(0.318)
Vestibular complex, superior nucleus	26	0.256	0.208	23	0.277	0.201
	(25)	(0.284)	(0.168)	(22)	(0.276)	(0.214)
Eye surface, half	28	−0.017	0.932	24	−0.046	0.831
	(27)	(−0.004)	(0.985)	(23)	(−0.046)	(0.835)
Testes weight	26	0.106	0.607	24	−0.100	0.642
	(25)	(0.213)	(0.306)	(23)	(−0.079)	(0.721)

n, sample size; r, correlation coefficient (Pearson's r); P, χ^2 probability that correlation is due to random chance. Values in parentheses are the same calculations as those in the line above with the data point for *Homo sapiens* removed from the data set; boldface type indicates that the correlation is statistically significant at the 0.05 confidence level.
*See text for definition of residual.

life-span. By contrast, the hippocampus and lateral geniculate nucleus correlate with female reproductive age but do not correlate with life-span.

Brain Structures and Life-Span in Strepsirhines. In strepsirhines, brain weight is not significantly correlated with either life-span or female reproductive age when the effect of body size is removed (1); however, the volumes of some brain structures are correlated. The centromedial complex of the

amygdala (see Fig. 2), the globus pallidus ($n = 8$, $r = 0.771$, $P = 0.026$), and the subthalamus ($n = 8$, $r = 0.759$, $P = 0.030$) are significantly, positively correlated with life-span in strepsirhines.

Brain Structures and Reproductive Age in Strepsirhines. There are no brain structures that are significantly, positively correlated with female reproductive age in strepsirhines, but the triangular nucleus of the septum ($n = 9$, $r = -0.709$, $P =$

FIG. 1.   Life-span residuals vs. residuals for volumes of several brain structures in haplorhine primates. The lines were fit by using a major axis regression because it provides more accurate estimation of the true slope (17). Symbols indicate the primary diet type of the species in question. (A) Life-span residuals vs. cerebellar volume residuals ($n = 26$, $r = 0.750$, $P < 0.001$, slope = 1.124). (B) Life-span residuals vs. neocortical volume residuals ($n = 26$, $r = 0.621$, $P = 0.001$, slope = 0.839). (C) Life-span residuals vs. amygdala volume residuals ($n = 23$, $r = 0.623$, $P = 0.001$, slope = 1.392). (D) Life-span residuals vs. hypothalamic volume residuals ($n = 15$, $r = 0.595$, $P = 0.019$, slope = 2.170).

0.033), the vestibular complex as a whole ($n = 9$, $r = -0.711$, $P = 0.032$), and the medial ($n = 9$, $r = -0.741$, $P = 0.023$) and lateral ($n = 9$, $r = -0.788$, $P = 0.012$) vestibular nuclei considered separately are significantly, negatively correlated with female reproductive age. These structures are larger in early maturing strepsirhine primates.

DISCUSSION

The brain is a mosaic with respect to the life-cycle parameters of maximum recorded life-span and female reproductive age. When the effect of body weight is removed, the medulla and most first-order sensory structures are not correlated with either life-span or female reproductive age in haplorhine primates. Presumably these structures have little to do with the lifelong storage of information that might enhance survivability. Many other brain structures are correlated with both measures of the adult life cycle, which agrees with our findings for the brain as a whole (1). The correlated cortical and cerebellar structures probably do participate in the long-term memory storage that might be used to survive critical changes in the animal's environment that might be expected to occur during a long life-span (1).

The cerebellum is the brain structure that is best correlated with life-span, and it is intriguing to note that parts of the cerebellum undergo substantial age-related reduction in mass (19). Data from a recent magnetic resonance imaging study suggest that there is a 25–30% shrinkage of the declive, folium, tuber, and pyramis lobes of the cerebellar vermis from age 20 to age 70 (19). Cerebellar Purkinje cells are particularly vulnerable to destruction in alcoholics but also show age-related loss in subjects without a history of alcohol intoxication (20). Purkinje cells maintain a high level of spontaneous activity (21), which may be responsible for their vulnerability to toxins and other pathophysiological states. We speculate that in the normal course of life, primates might be exposed to toxins in their diet that would cause the loss of Purkinje cells and cerebellar mass. Because loss of cerebellar function would be strongly selected against in tree-dwelling primates, there might be an over-production of cerebellar neurons during development to compensate for loss due to exposure to dietary toxins during the course of life.

By contrast, the hippocampus and the lateral geniculate nucleus significantly correlate with female reproductive age but do not correlate with life-span. We have no explanation for these apparently anomalous findings.

Neurobiology: Allman *et al.*

Proc. Natl. Acad. Sci. USA 90 (1993) 3563

FIG. 2. Life-span residuals vs. residuals of volume of the centromedial complex of the amygdala for strepsirhine primates ($n = 13$, $r = 0.581$, $P = 0.038$, slope $= 1.991$). A major axis regression line was used here as in Fig. 1.

The centromedial complex of the amygdala is the only structure to correlate with life-span in both strepsirhine and haplorhine primates. However, it should be noted that statistical significance of the haplorhine correlation depends on inclusion of the human data point. The correlation is significant for primates as a whole (including the human, $r = 0.544$, $P = 0.001$; without the human, $r = 0.411$, $P = 0.013$). The medial part of amygdala, including this structure, contains many senile plaques in old rhesus monkeys (22), degenerates in Alzheimer disease (23, 24), and has even been suggested as the initial site of degenerative changes in Alzheimer disease (24). The centromedial complex of the amygdala is the principal source of amygdalar input to the hypothalamus and, thus, is a major source of telencephalic input to the neuroendocrine system (25, 26). The central nucleus of the amygdala participates in the regulation of blood pressure and the stress response (26–28). Disruption of these regulatory functions, as a consequence of degeneration of the centromedial complex of the amygdala, could be crucial to the aging process and a key factor in determining life-span.

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