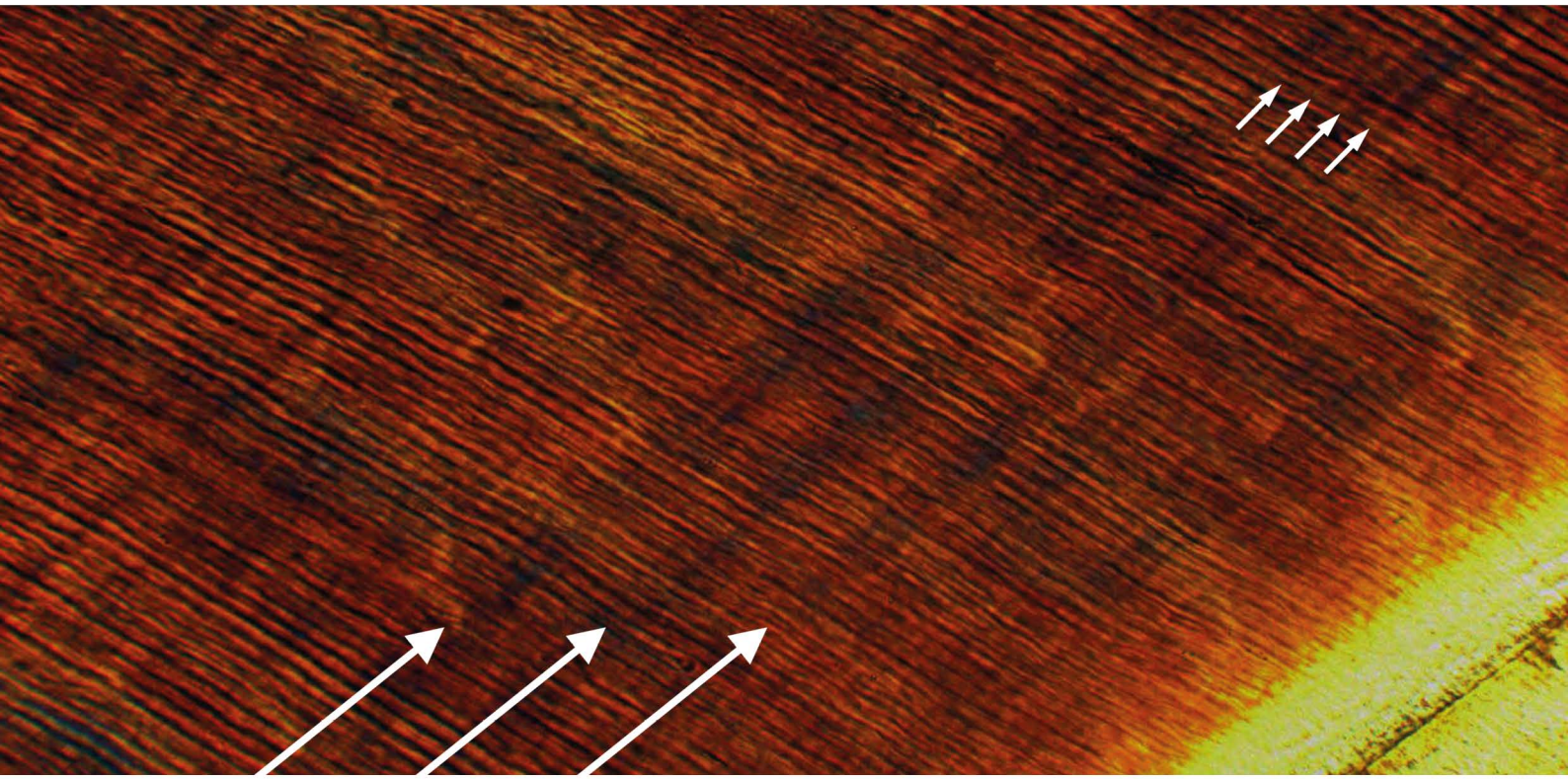

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The Havers–Halberg oscillation regulates primate tissue and organ masses across the life-history continuum

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Long period biological timing, as deduced from a primate enamel formation rhythm termed the repeat interval (RI), varies predictably with body size and primate life-history characteristics. RI is a manifestation of a fundamental metabolic rhythm termed the Havers–Halberg oscillation (HHO). Because body size is highly associated with RI (and the HHO), we assume that RI should also have relationships with primate tissue and organ masses that likely covary with body size. We evaluate body mass and constituent tissue and organ masses, as well as basal metabolic rate (BMR), for twelve primate taxa. Regressing RI against tissue, organ, and body masses, as well as BMR, we find the relationships to be significant. Partial correlations controlling for the effects of either body mass or fat-free body mass suggest that the significant associations that tissue and organ masses have with each other are likely related to their dependence on body size in general. Body mass and most tissue masses approximate 1/4 scaling. However, brain mass has a singularly high slope in relation to RI. The relatively slow growth of other tissue and organ masses with increasing RI may provide 'payment' for the high mass specific metabolic rate of the brain.

ADDITIONAL KEYWORDS: body mass – body size – enamel striae of Retzius – metabolism – expensive tissue hypothesis.

INTRODUCTION

Fundamental to an organism's life history is its body mass (Schmidt-Nielsen, 1984; Calder, 1996). In the search for proximate mechanisms, it has been shown that long period biological timing, as deduced from the enamel formation rhythms evident in its micro-anatomy, varies predictably with body size (Bromage *et al*., 2009). Although it is well known that the enamel structure of primates (and many other mammals) manifests as a daily developmental event, a previously enigmatic long period rhythm is also visible, known as the stria of Retzius. The number of daily events between adjacent striae of Retzius is termed the repeat interval (RI), which ranges in primates from 2 to 11 days; the larger the primate, the longer its RI.[†]

Through its influence on body size, RI is highly related to all common primate life-history timing (e.g. age at sexual maturity, lifespan) and mass characteristics (e.g. neonatal body mass, adult brain weight), together with basal and specific metabolic rates. One life-history characteristic, oestrous length, is related to RI only when examined independent of body size (Bromage *et al*., 2012). The pattern of body size-dependent and -independent characteristics aligns with hypothalamic controls over anterior and posterior pituitary function, respectively, suggesting that long period biological timing is fundamental to a metabolism-mediated regulation of primate life history (Bromage *et al*., 2012). Given this key role, we termed this period the Havers–Halberg oscillation (HHO) (Bromage *et al*., 2009), in reference to Clopton Havers, a 17th Century hard tissue anatomist (Havers, 1691), and Franz Halberg, a long-time explorer of long-period rhythms (Halberg *et al*., 1965).

It stands to reason that, through its relationship with body size, RI (and the HHO) should also have relationships with primate tissue and organ masses

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[†]Another term soon to be promulgated in the literature is 'repeat period' (RP). Further, the biological process – or the Havers–Halberg Oscillation – that this period represents requires a new term to describe this category of rhythm, which we call 'multidien', referring to a many-days rhythm.

that contribute to (and thus likely covary with) body size. Navarrete *et al*. (2012) recently compiled tissue and organ masses for a variety of primates and other mammals, and thus we aimed to determine the extent to which RI would remain statistically tethered to the body's constituent parts.

MATERIALS AND METHODS

We evaluated the compilation of tissue, organ, and body masses and basal metabolic rate (BMR; both body mass derived, BMR-BM, and in relation to oxygen consumed, BMR-O_2) provided by Navarrete *et al*. (2012) for primate taxa whose RI have been reported previously (Bromage *et al*., 2012). Twelve taxa satisfy the requirements (Table 1). Most life-history traits associate together by allometric scaling laws because they have been observed to scale with body mass. We thus log-transformed all data.

Our first interest lay in regressing RI against tissue and organ masses, body mass, fat-free body mass, and BMR (Table 2), and in providing a measure of the extent to which RI is an appropriate predictor variable for these mass and metabolic variables.

Because RI has been previously shown to significantly relate to primate body mass in a simple linear fashion, we tested whether the same might be true for RI and its relationships with tissue, organ, and body masses, as well as BMR. As such, we took the residuals arising from the regression of primate RI versus body mass against tissue, organ, and body masses, as well as BMR.

Finally, our interest also lay in describing the extent to which tissue and organ masses are integrated, and thus we performed correlation matrices on log-transformed and ranked log-transformed data (Tables 3, 4), in addition to performing a series of partial correlations, controlling for each variable.

All statistics were performed using SPSS, version 21 (IBM Corporation). Linear and multiple regressions were executed using the least squares model and reporting the Pearson product-moment correlation coefficient (r) and its statistical significance (P), as well as the adjusted coefficient of determination (R^2). Correlation reporting included r, P, and the number of pairwise cases (N) or, in the case of partial correlation, the reporting of degrees of freedom (d.f.). $P \leq 0.050$ was considered statistically significant. Some tests were performed with and without primate taxa having an RI of only 1 day (RI = 1) for reasons explained previously Bromage *et al*. (2012).

RESULTS

Upon regressing RI against tissue, organ, and body masses, as well as BMR, we find the relationships to be globally high and significant (Table 2). Thus, as previously reported for body mass, RI has very high explanatory value with respect to predicting the tissue and organ masses that contribute to body mass.

Linear regressions of the residuals arising from the regression of primate RI versus body mass against tissue, organ, and body masses, as well as BMR, failed to reveal any significant linear or nonlinear association with fat-free body mass, organ and tissue masses, or BMR (data not shown). This suggests that there is a simple linear relationship between RI and body, organ, and tissue mass, as well as BMR.

Correlation matrices of all variables, using either the log-transformed data or ranked log-transformed data, indicate that each variable is significantly and highly correlated with every other variable (Tables 3, 4); only adipose depot failed to reveal associations with BMR variables when using ranked data.

Partial correlations were performed, with each variable serving as a control to remove their respective effects on correlations between the other variables (data not shown). Almost all of the tests performed using all taxa revealed a broad lack of associations between variables (i.e. correlation matrices with comparatively few significant and strong relationships). However, when controlling for either RI or adipose depot, many associations remain high and statistically significant.

DISCUSSION

Life history is an integrative field of study, which concerns the pace and pattern of life. It includes such developmental traits as gestation length, age at weaning and sexual maturity, and lifespan, coupled with various measures of size such as body mass, birth weight, and brain weight. The coupling of developmental timing and size renders a life-history matrix packaged so tightly together that no single trait appears free to vary without corresponding relative changes in the others (Harvey & Clutton-Brock, 1985).

The present study has confirmed high degrees of association between RI, tissue and organ masses, body mass, fat-free body mass, and BMR, similar to those found between RI and life-history characteristics (Bromage *et al*., 2012) (Tables 3, 4). Nevertheless, when all of the taxa reported in Table 1 are considered, and partial correlation matrices are calculated controlling for the effects of either body mass or fat-free body mass, few significant relationships between variables endure. This would suggest that the significant associations that tissue and organ masses have with each other is likely related to their dependence on body size in general.

Table 1. Data employed in the present study include primate tissue and organ masses, body mass, fat-free body mass, and basal metabolic rate (Navarrete *et al.*, 2012), as well as primate enamel repeat intervals (Bromage *et al.*, 2012)

Genus species	*Alouatta sara*	*Callithrix jacchus*	*Cebuella pygmaea*	*Cebus apella*	*Hylobates concolor*	*Leontopithecus chrysomelas*	*Papio hamadryas*	*Saguinus fuscicollis lagonotus*	*Saguinus oedipus*	*Saimiri boliviensis*	*Symphalangus syndactylus*	*Theropithecus gelada*
Number and sex	1 F	1 M	1 F	1 F	1 F	3 M	2 M	1 M	1 F/1 M	1 M	1 M	1 M
Repeat interval	6	1	1	4.5	4	3	7	2	1	3	4.5	7
Log repeat interval	0.78	0	0	0.65	0.6	0.48	0.85	0.3	0	0.48	0.65	0.85
Log repeat interval number 1	0.78			0.65	0.6	0.48	0.85	0.3		0.48	0.65	0.85
Body mass	4400	311.6	163	1750	6550	641.67	23 250	330	624	1003	8500	11400
Log body mass	3.64	2.49	2.21	3.24	3.82	2.81	4.37	2.52	2.8	3	3.93	4.06
Log RI residuals	0.15	−0.17	−0.05	0.18	−0.1	0.18	−0.08	0.12	−0.29	0.1	−0.09	0.05
Log RI residuals number 1	0.11			0.09	−0.11	0.03	−0.01	−0.07		−0.02	−0.09	0.07
Fat-free body mass	4325.71	306.06	141.05	1574.3	6475.67	586.16	22 243.17	318.82	560.8	986.42	7913.4	10938.3
Log fat-free body mass	3.64	2.49	2.15	3.2	3.81	2.77	4.35	2.5	2.75	2.99	3.9	4.04
Log fat-free body mass residuals	0.14	−0.18	−0.04	0.19	−0.11	0.19	−0.08	0.12	−0.28	0.1	−0.09	0.05
Log fat-free body mass residuals number 1	0.11			0.1	−0.11	0.03	−0.01	−0.07		−0.02	−0.09	0.07
Brain mass	56.46	7.25	4.4	50.76	137.79	13.21	173.92	7.77	9.97	29.01	142.97	140.9
Log brain mass	1.75	0.86	0.64	1.71	2.14	1.12	2.24	0.89	1	1.46	2.16	2.15
Heart mass	24	2.83	0.86	13.38	58.19	3.82	103.16	3.3	3.68	6.47	51.45	77.22
Log heart mass	1.38	0.45	−0.07	1.13	1.76	0.58	2.01	0.52	0.57	0.81	1.71	1.89
Lung mass	47.63	4.66	1.86	29.3	135.64	8.61	253.56	3.84	7.45	7.8	115.79	173.87
Log lung mass	1.68	0.67	0.27	1.47	2.13	0.94	2.4	0.58	0.87	0.89	2.06	2.24
Kidney mass	9.86	2.94	1.91	10.4	35.21	4.13	80.31	1.93	3.15	6.7	43.72	38.04
Log kidney mass	0.99	0.47	0.28	1.02	1.55	0.62	1.9	0.29	0.5	0.83	1.64	1.58
Liver mass	81.21	17.84	13.49	49.28	293	18.92	392.02	14.35	20.89	19.43	293.72	235.52
Log liver mass	1.91	1.25	1.13	1.69	2.47	1.28	2.59	1.16	1.32	1.29	2.47	2.37
Digtract mass	113.35	10.8	6.96	44.41	344.53	15.01	458.67	9.66	12.67	25.3	406.85	361.45
Log digtract mass	2.05	1.03	0.84	1.65	2.54	1.18	2.66	0.98	1.1	1.4	2.61	2.56
Stomach mass	32.21	1.39	0.76	7.98	94.1	3.71	86.42	1.31	2.35	5.95	138.46	51.94
Log stomach mass	1.51	0.14	−0.12	0.9	1.97	0.57	1.94	0.12	0.37	0.77	2.14	1.72
Intestine mass	81.14	9.41	6.2	36.43	250.43	11.3	372.25	8.35	10.32	19.35	268.39	309.51
Log intestine mass	1.91	0.97	0.79	1.56	2.4	1.05	2.57	0.92	1.01	1.29	2.43	2.49
Spleen mass	6.17	0.54	0.18	1.25	25.45	1.1	26.78	0.36	0.33	1.09	22.71	9.31
Log spleen mass	0.79	−0.27	−0.74	0.1	1.41	0.04	1.43	−0.44	−0.48	0.04	1.36	0.97
Visceral mass	282.22	39.61	25.26	148.02	892.02	51.6	1 314.48	33.44	48.15	66.79	934.24	895.41
Log visceral mass	2.45	1.6	1.4	2.17	2.95	1.71	3.12	1.52	1.68	1.82	2.97	2.95
Adipose depot	74.29	5.54	21.95	175.7	74.33	55.5	1 006.83	11.18	63.2	16.58	586.6	461.7
Log adipose depot	1.87	0.74	1.34	2.24	1.87	1.74	3	1.05	1.8	1.22	2.77	2.66
BMR-BM	4670	190	140.6			733	15 900		296	850		
Log BMR-BM	3.67	2.28	2.15			2.87	4.2		2.47	2.93		
BMR-O_2	2000.3	157.7	99.8			382	5 066.6		265.5	592		
Log BMR-O_2	3.3	2.2	2			2.58	3.7		2.42	2.77		

BMR, basal metabolic rate (both body mass derived, BMR-BM, and in relation to oxygen consumed, BMR-O_2); RI, repeat interval; M, male; F, female.

Table 2. Summary statistics of the regressions of log repeat interval (RI) with log-transformed body and tissue masses and metabolic rate

Tests of association	Regression variation*	R value	P value	R^2 value (adjusted)	Slope
RI/Body mass (g)	w/RI = 1	0.882	< 0.001	0.755	0.40
	w/o RI = 1	0.899	0.001	0.781	0.27
RI/Fat-free body mass (g)	w/RI = 1	0.883	< 0.001	0.757	0.40
	w/o RI = 1	0.896	0.001	0.774	0.26
RI/Brain mass (g)	w/RI = 1	0.896	< 0.001	0.782	0.49
	w/o RI = 1	0.829	0.011	0.635	0.31
RI/Heart mass (g)	w/RI = 1	0.879	< 0.001	0.747	0.42
	w/o RI = 1	0.858	0.003	0.699	0.28
RI/Lung mass (g)	w/RI = 1	0.862	< 0.001	0.717	0.38
	w/o RI = 1	0.875	0.002	0.732	0.24
RI/Kidney mass (g)	w/RI = 1	0.829	0.001	0.657	0.47
	w/o RI = 1	0.811	0.008	0.609	0.28
RI/Liver mass (g)	w/RI = 1	0.786	0.002	0.579	0.44
	w/o RI = 1	0.792	0.011	0.575	0.25
RI/Digestive tract mass (g)	w/RI = 1	0.846	0.001	0.686	0.38
	w/o RI = 1	0.822	0.007	0.630	0.23
RI/Stomach mass (g)	w/RI = 1	0.850	< 0.001	0.694	0.34
	w/o RI = 1	0.782	0.013	0.566	0.20
RI/Intestinal mass (g)	w/RI = 1	0.843	0.001	0.681	0.39
	w/o RI = 1	0.832	0.005	0.647	0.23
RI/Spleen mass (g)	w/RI = 1	0.835	0.001	0.667	0.34
	w/o RI = 1	0.750	0.020	0.500	0.19
RI/Visceral mass (g)	w/RI = 1	0.834	0.001	0.666	0.41
	w/o RI = 1	0.827	0.006	0.638	0.25
RI/Adipose depot (g)	w/RI = 1	0.753	0.005	0.524	0.34
	w/o RI = 1	0.840	0.005	0.683	0.23
RI/ BMR-BM	w/RI = 1	0.952	0.001	0.888	0.47
	w/o RI = 1	0.978	0.022	0.934	0.30
RI/BMR-O_2	w/RI = 1	0.937	0.002	0.853	0.57
	w/o RI = 1	0.970	0.003	0.912	0.37

*In all tests of association between RI and primate traits, regressions were performed with (w/) and without (w/o) RI = 1 taxa if present in the data set.
BMR, basal metabolic rate (both body mass derived, BMR-BM, and in relation to oxygen consumed, BMR-O_2).

Previously, we observed that RI = 1 primates skewed the results of relationships between primate life-history characteristics because of their having relatively larger bodies and brains and longer gestation and lactation lengths, etc., than generally expected for their RI (Bromage *et al*., 2012) It was argued that, to evolve the full spectrum of primate life characterizing the primate order today, taxa evolved HHO variability as the biological timing mechanism by which life histories are regulated at larger body masses. Because of this potential anomaly, we also aimed to determine whether the results of tests of relationships between tissue and organ masses might differ when choosing only RI ≥ 2 taxa for analysis. When controlling for the effects of either body mass or fat-free body mass, we found that, as for previous tests including RI = 1 taxa, few relationships between variables were forthcoming.

Bromage *et al*. (2012) reported that 'RI is a response to an oscillation postulated by us to regulate body mass, and through this relationship, much of the life history matrix' (p. 137). That RI loses wholesale its relationships to life-history characteristics when controlling for body mass is evidence that the HHO is a key variable responsible for variation in body mass and, with that result, variability in life history. The importance of mass has been a major focus: 'Such covariation (between life history characteristics) implies that all life histories may be determined by some key variable. Many possibilities have been suggested, including brain size, metabolic rate, and even an elusive *"periodengeber" which entrains the timing of life history events to body weight*' (p. 23; parentheses and italics ours). We highlight the latter part of this quote, and claim that the HHO is the elusive 'periodengeber'. As explained previously (Bromage

Table 3. Correlation matrix of repeat interval (RI) and body, tissue, and organ masses, as well as basal metabolic rate (BMR)

Variables		1 RI ≥ 2	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1 RI	*r*	1	0.882†	0.883†	0.896†	0.878†	0.862†	0.829†	0.786†	0.846†	0.850†	0.843†	0.835†	0.834†	0.753†	0.952†	0.937†
	Significance		0.000	0.000	0.000	0.000	0.000	0.001	0.002	0.001	0.000	0.001	0.001	0.001	0.005	0.001	0.002
	N	9	12	12	12	12	12	12	12	12	12	12	12	12	12	7	7
2 Body mass	*r*	0.899†	1	1.000†	0.979†	0.989†	0.990†	0.975†	0.963†	0.981†	0.970†	0.981†	0.956†	0.982†	0.865†	0.984†	0.990†
	Significance	0.001		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	N	9		12	12	12	12	12	12	12	12	12	12	12	12	7	7
3 Fat-free body mass	*r*	0.896†		1	0.979†	0.991†	0.989†	0.974†	0.962†	0.981†	0.970†	0.981†	0.959†	0.981†	0.853†	0.984†	0.991†
	Significance	0.001			0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	N	9			12	12	12	12	12	12	12	12	12	12	12	7	7
4 Brain mass	*r*	0.845†			1	0.983†	0.978†	0.975†	0.952†	0.980†	0.978†	0.977†	0.956†	0.976†	0.827†	0.983†	0.993†
	Significance	0.004				0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.000	0.000
	N	9				12	12	12	12	12	12	12	12	12	12	7	7
5 Heart mass	*r*	0.858†				1	0.991†	0.968†	0.964†	0.982†	0.968†	0.982†	0.960†	0.982†	0.817†	0.973†	0.984†
	Significance	0.003					0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.000	0.000
	N	9					12	12	12	12	12	12	12	12	12	7	7
6 Lung mass	*r*	0.875†					1	0.975†	0.978†	0.985†	0.970†	0.986†	0.961†	0.990†	0.859†	0.973†	0.975†
	Significance	0.002						0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	N	9						12	12	12	12	12	12	12	12	7	7
7 Kidney mass	*r*	0.811†						1	0.975†	0.980†	0.963†	0.981†	0.959†	0.984†	0.859†	0.946†	0.945†
	Significance	0.008							0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.001
	N	9							12	12	12	12	12	12	12	7	7
8 Liver mass	*r*	0.792*							1	0.989†	0.966†	0.990†	0.965†	0.995†	0.842†	0.936†	0.928†
	Significance	0.011								0.000	0.000	0.000	0.000	0.000	0.001	0.002	0.003
	N	9								12	12	12	12	12	12	7	7
9 Digestive tract mass	*r*	0.822†								1	0.987†	0.999†	0.979†	0.998†	0.829†	0.982†	0.981†
	Significance	0.007									0.000	0.000	0.000	0.000	0.001	0.000	0.000
	N	9									12	12	12	12	12	7	7
10 Stomach mass	*r*	0.782*									1	0.978†	0.985†	0.980†	0.810†	0.995†	0.999†
	Significance	0.013										0.000	0.000	0.000	0.001	0.000	0.000
	N	9										12	12	12	12	7	7
11 Intestine mass	*r*	0.832†										1	0.972†	0.998†	0.832†	0.973†	0.972†
	Significance	0.005											0.000	0.000	0.001	0.000	0.000
	N	9											12	12	12	7	7
12 Spleen mass	*r*	0.750*											1	0.975†	0.762†	0.984†	0.976†
	Significance	0.020												0.000	0.004	0.000	0.000
	N	9												12	12	7	7
13 Visceral mass	*r*	0.827†												1	0.844†	0.972†	0.969†
	Significance	0.006													0.001	0.000	0.000
	N	9													12	7	7
14 Adipose depot	*r*	0.840†													1	0.823*	0.806*
	Significance	0.005														0.023	0.029
	N	9														7	7
15 BMR-BM	*r*	0.978*														1	0.995†
	Significance	0.022															0.000
	N	4															7
16 BMR-O_2	*r*	0.970*															1
	Significance	0.030															
	N	4															

Comparisons are for all taxa except the vertical column, 1 RI ≥ 2, which includes all but RI = 1 taxa.
*Correlation is significant at the 0.05 level (two-tailed).
†Correlation is significant at the 0.01 level (two-tailed).
BMR, basal metabolic rate (both body mass derived, BMR-BM, and in relation to oxygen consumed, BMR-O_2).

Table 4. Correlation matrix of ranked repeat interval (RI) and body, tissue, and organ masses, as well as basal metabolic rate (BMR)

Variables		1 RI ≥ 2	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1 RI	*r*	1	0.931†	0.931†	0.910†	0.920†	0.906†	0.885†	0.814†	0.896†	0.811†	0.917†	0.867†	0.896†	0.821†	0.941†	0.941†
	Significance		0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.000	0.001	0.000	0.000	0.000	0.001	0.002	0.002
	N	9	12	12	12	12	12	12	12	12	12	12	12	12	12	7	7
2 Body mass	*r*	0.890†	1	1.000†	0.993†	0.993†	0.979†	0.979†	0.951†	0.986†	0.937†	0.993†	0.937†	0.986†	0.888†	0.971†	0.971†
	Significance	0.001		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	N	9		12	12	12	12	12	12	12	12	12	12	12	12	7	7
3 Fat-free body mass	*r*	0.890†		1	0.993†	0.993†	0.979†	0.979†	0.951†	0.986†	0.937†	0.993†	0.937†	0.986†	0.888†	0.971†	0.971†
	Significance	0.001			0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	N	9			12	12	12	12	12	12	12	12	12	12	12	7	7
4 Brain mass	*r*	0.843†			1	0.979†	0.965†	0.986†	0.965†	0.993†	0.958†	0.986†	0.944†	0.993†	0.895†	0.971†	0.971†
	Significance	0.004				0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	N	9				12	12	12	12	12	12	12	12	12	12	7	7
5 Heart Mass	*r*	0.866†				1	0.986†	0.965†	0.944†	0.972†	0.930†	0.986†	0.944†	0.972†	0.867†	0.971†	0.971†
	Significance	0.003					0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	N	9					12	12	12	12	12	12	12	12	12	7	7
6 Lung mass	*r*	0.865†					1	0.965†	0.944†	0.972†	0.930†	0.986†	0.958†	0.972†	0.874†	0.943†	0.943†
	Significance	0.003						0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.001
	N	9						12	12	12	12	12	12	12	12	7	7
7 Kidney mass	*r*	0.821†						1	0.965†	0.993†	0.958†	0.986†	0.944†	0.993†	0.902†	0.946†	0.946†
	Significance	0.007							0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.001	0.001
	N	9							12	12	12	12	12	12	12	7	7
8 Liver mass	*r*	0.798†							1	0.972†	0.958†	0.958†	0.916†	0.972†	0.902†	0.900†	0.900†
	Significance	0.010								0.000	0.000	0.000	0.000	0.000	0.000	0.006	0.006
	N	9								12	12	12	12	12	12	7	7
9 Digestive tract mass	*r*	0.843†								1	0.965†	0.993†	0.951†	1.000†	0.888†	0.965†	0.965†
	Significance	0.004									0.000	0.000	0.000	0.000	0.000	0.000	0.000
	N	9									12	12	12	12	12	7	7
10 Stomach mass	*r*	0.667*									1	0.944†	0.944†	0.965†	0.839†	0.990†	0.990†
	Significance	0.050										0.000	0.000	0.000	0.001	0.000	0.000
	N	9										12	12	12	12	7	7
11 Intestine mass	*r*	0.887†										1	0.944†	0.993†	0.881†	0.965†	0.965†
	Significance	0.001											0.000	0.000	0.000	0.000	0.000
	N	9											12	12	12	7	7
12 Spleen mass	*r*	0.748*											1	0.951†	0.804†	0.909†	0.909†
	Significance	0.020												0.000	0.002	0.005	0.005
	N	9												12	12	7	7
13 Visceral mass	*r*	0.843†												1	0.888†	0.965†	0.965†
	Significance	0.004													0.000	0.000	0.000
	N	9													12	7	7
14 Adipose depot	*r*	0.857†													1	0.726	0.726
	Significance	0.003														0.064	0.064
	N	9														7	7
15 BMR-BM	*r*	0.939														1	1.000†
	Significance	0.061															0.000
	N	4															7
16 BMR-O_2	*r*	0.939															1
	Significance	0.061															
	N	4															

Comparisons are for all taxa except the vertical column, 1 RI ≥ 2, which includes all but RI = 1 taxa.
*Correlation is significant at the 0.05 level (two-tailed).
†Correlation is significant at the 0.01 level (two-tailed).
BMR, basal metabolic rate (both body mass derived, BMR-BM, and in relation to oxygen consumed, BMR-O_2).

Table 5. Primate tissue, organ, and body masses, as well as basal metabolic rate (BMR), from Table 2 are sorted into arbitrary groups with slopes below 0.25, slopes of 0.25–0.29, and slopes of 0.30 and higher

Relationships with slopes below 0.25	Relationships with slopes of 0.25–0.29	Relationships with slopes of 0.30 and above
RI/Digestive tract mass (g) = 0.23	RI/Body mass (g) = 0.27	RI/Brain mass (g) = 0.31
RI/Stomach mass (g) = 0.20	RI/Fat-free body mass (g) = 0.26	RI/BM BMR = 0.30
RI/Intestinal mass (g) = 0.23	RI/Heart mass (g) = 0.28	RI/BMR (mL O_2 h^{-1}) = 0.37
RI/Lung mass (g) = 0.24	RI/Kidney mass (g) = 0.28	
RI/Spleen mass (g) = 0.19	RI/Liver mass (g) = 0.25	
RI/Adipose depot (g) = 0.23	RI/Visceral mass (g) = 0.25	
Mean slope = 0.22	Mean slope = 0.27	

BMR, basal metabolic rate (both body mass derived, BMR-BM, and in relation to oxygen consumed, BMR-O_2); RI, repeat interval.

et al., 2012), '. . . we conjecture that (hypothalamic nuclei) transmit signals . . . to regulate body mass and, through the set of SCN-integrated hypothalamic nuclei, to regulate life history . . . This is the basis for covariation of life history characteristics . . .' (p. 142).

However, apart from its hypothesized hypothalamic regulation of life history, what has not been properly discussed is how life-history variability and covariation would manifest through the control of body mass by HHO. This topic requires dedicated review but, for consideration here, we offer the following loosely formulated relationships in respect of each primate life-history characteristic: gestation length and lactation length are a function of the mass of the mother and are coupled by metabolic rate-dependent energy allocations to offspring (Dubman, Collard & Mooers, 2012); age at sexual maturity (and we presume age at first breeding) depends upon having reached a body mass able to metabolically support a foetus to full term (adolescent subfecundity acknowledged) at an age linked to extrinsic mortality risk (Ricklefs, 2010); interbirth interval, in a finite metabolic model, depends upon the duration of the recouping period and the return of metabolic balance and, because BMR depends upon mass, so does interbirth interval – the mass dependence of primate interbirth interval has been long examined (Harvey, Clutton-Brock & Martin, 1987), although brain size in a study of New World monkeys has also been implicated (Fedigan & Rose, 1995); lifespan is a function of rates of cell proliferation known to regulate longevity (Magalhães & Faragher, 2008) and mass-dependent extrinsic mortality risk (Ricklefs, 2010). In sum, body mass is a function of cell proliferation rates and, because these rates are a direct expression of the pace of life history, we find this consistent with the hypothesis recently set forth, namely that the HHO regulates cell proliferation rate rhythms, which build mass in appropriate units of time across the life-history continuum (Bromage *et al*., 2012).

In their evaluation of the 'expensive tissue hypothesis' previously advanced by Aiello & Wheeler (1995), Navarrete *et al*. (2012) hypothesized that, during the course of primate evolution, the digestive tract, which has a relatively high mass-specific metabolic rate, diminished in proportion to body mass to provide a finite energetic trade-off in support of the development and function of a relatively larger brain, another such 'expensive' tissue. However, Navarrete *et al*. (2012) failed to find the expected negative relationship between the size of the digestive tract and brain size when controlling for fat-free body mass. Instead, they found that the adipose depot and brain size were negatively correlated, indicating that the degree of encephalization and adiposity are compensatory strategies to buffer against starvation.

Slopes of the regressions of RI with body and tissue masses shed additional light on the scaling relationships among covarying body mass characteristics (which has consequence for life history). The slope arithmetic mean for body and tissue masses RI ≥ 2 is 0.25, equal to the slope with 1/4 power that typifies some relationships between life-history characteristics and body size. However, body and tissue masses from Table 2 can be sorted into arbitrary groups with slopes below 0.25 (spleen, stomach, adipose depot, digestive tract, intestinal, lung), with slopes of 0.25–0.29 (liver, viscera, fat-free body, body, heart, kidney), and with slopes of 0.30 and higher (brain, BMR) (Table 5). Body mass and most tissue masses approximate 1/4 scaling. However, brain mass has a singularly high slope in relation to RI, meaning that, as body and most tissue masses increase, brain tissue increases relatively faster. 'Payment' for this in a finite energetic model would require some tissue masses to increase more slowly relative to body size, such as those in the arbitrary group with slopes below 0.25. We are thus led to consider that, when assessed in relationship with HHO metabolic rhythms regulating body mass and governing life history, both the

digestive tract and the adipose depot scale in a manner consistent with the expensive tissue hypothesis.

The high slopes of RI regressed against metabolic rate suggest that the finite energetic model must be amended to allow for increased consumption, and/or changes to metabolic efficiency, and/or changes to the way that energy is allocated at larger body sizes. Our previous work on RI in relation to primate life-history traits provides clear evidence indicating that a slowing down of the pace of life history reflects a primate metabolic adaptation at increased body size. For example, gestation length, age at first breeding, and interbirth interval all have remarkably high slopes of 0.50 and greater (Bromage *et al*., 2012), suggesting that primates space their production energy over increasingly longer periods of time as primate taxa increase the length of their HHO biological timing and body size.

Conclusions

We conclude that primate RI, which is a manifestation of the HHO, is highly and significantly related to body mass, as well as to the constituent tissue and organ masses that make up the body. We suggest that the HHO among primates is a metabolic rhythm controlling the pace of development and life history through its primary function to accrue adult body mass.

The relatively slow growth of many tissues, organs, and body masses with increasing RI suggests that it would be rewarding to investigate why primate bodies are so small relative to their brains versus the almost universal effort presently undertaken to explain why their brains are so large in relation to body size.

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