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Primate enamel evinces long period biological timing and regulation of life history

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ABSTRACT

The factor(s) regulating the combination of traits that define the overall life history matrix of mammalian species, comprising attributes such as brain and body weight, age at sexual maturity, lifespan and others, remains a complete mystery. The principal objectives of the present research are (1) to provide evidence for a key variable effecting life history integration and (2) to provide a model for how one would go about investigating the metabolic mechanisms responsible for this rhythm. We suggest here that a biological rhythm with a period greater than the circadian rhythm is responsible for observed variation in primate life history. Evidence for this rhythm derives from studies of tooth enamel formation. Enamel contains an enigmatic periodicity in its microstructure called the striae of Retzius, which develops at species specific intervals in units of whole days. We refer to this enamel rhythm as the repeat interval (RI). For primates, we identify statistically significant relationships between RI and all common life history traits. Importantly, RI also correlates with basal and specific metabolic rates. With the exception of estrous cyclicity, all relationships share a dependence upon body mass. This dependence on body mass informs us that some aspect of metabolism is responsible for periodic energy allocations at RI timescales, regulating cell proliferation rates and growth, thus controlling the pace, patterning, and co-variation of life history traits. Estrous cyclicity relates to the long period rhythm in a body mass-independent manner. The mass-dependency and -independency of life history relationships with RI periodicity align with hypothalamic-mediated neurosecretory anterior and posterior pituitary outputs. We term this period the Havers-Halberg Oscillation (HHO), in reference to Clopton Havers, a 17th Century hard tissue anatomist, and Franz Halberg, a long-time explorer of long-period rhythms. We propose a mathematical model that may help elucidate the underlying physiological mechanism responsible for the HHO.

1. Synopsis

Because we are adding a novel dimension to life history research, which itself is already a complex field, upon reviewer recommendation we summarize here the main points of our contribution in more detail than is typically given in an abstract.

The pace and pattern of life is the subject of organismal life history, one of biology's most integrative disciplines. The life histories of mammals, for instance, are described by a number of characteristics, some of which relate to the timing and duration of life stages (e.g., age at sexual maturity, lifespan). Body and organ masses are also included in lists of mammalian life history characteristics because body size is fundamental to an organism's physiology and metabolic ecology (e.g., adult body mass, neonatal brain weight). What particularly interests researchers on the life histories of higher taxa, such as that of the order primates, is the covariation that exists between traits, but despite this interest, the factor(s) regulating and defining the overall life history matrix of mammals remain completely unknown.

Because metabolism is responsible for energy allocations that fuel all aspects of life history, metabolic rate is also included in the life history rubric. The stage is thus set for an investigation into the key variable(s) regulating an integrated and metabolism-mediated mammalian life history. We set forth the argument that, because all life history traits reflect dependence on rate and time, a biological timing mechanism must be invoked to help explain life history variation. Although much discussed, the daily, or circadian, biological clock cannot act as the mechanism by itself, because this timing is common even to mammals having magnificently disparate life structures.

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Mineralized tissue morphology, however, does provide insight into what these mechanisms might be. Mammalian enamel contains time-resolved incremental lines in its microanatomy, one of which represents a daily secretion rhythm, and the other, a long period secretion rhythm that presents at some multiple of daily events, called the stria of Retzius. The number of days between adjacent striae of Retzius is called the repeat interval (RI), the variation of which has recently been found to positively and significantly correlate with primate body mass, and which is also represented by lamellae in bone; we termed this period the "Havers-Halberg Oscillation" (HHO). Body mass is an important trait linked to life history, and so we sought here the potential that this rhythm may have for explaining the remainder of the primate life history gamut.

Correlation and regression statistics were used here to analyze the degrees of relationship between long period rhythms and life history traits, body and organ masses, and metabolic rates in the order primates. Several major outcomes are evident. The first is that RI is highly and significantly correlated with all life history characteristics except estrous cycle length, and with basal and specific metabolic rates (BMR and SMR, respectively). Also, when those primates having an RI of only one day (RI=1) – thus not presenting a long period rhythm – are removed from the data set, slopes of all regressions except that of SMR decrease and the statistical relationships often improve. Most intercorrelations are also high and significant, one major exception being the correlation between estrous cycle length and other life history traits and metabolic rates. Because of the profound influence that body mass exerts on mammalian life, statistical analyses were performed to control for its influence on the relationships between RI and the other characteristics examined. When so doing, estrous cycle length, which had previously exhibited itself as an outlier in all statistical tests, was found to be the only variable examined which presented high and significant correlations with RI. These results suggest that the HHO represented by RI exerts overarching control of organismal life history and metabolism by means of its regulation of body mass, while estrous cycle length is controlled in a body mass-independent manner.

Considering the nature of associations that RI has with life history characteristics and metabolism, we infer that periodic energy allocations at RI timescales regulate cell proliferation rates and growth, thus fueling life history and controlling the pace, patterning, and covariation of life history traits. The regulation of cell proliferation rates, which employs the circadian clock machinery, suggests a hypothalamic origin for the HHO, to include in its pathway the mammalian centrally regulated circadian clock localized to the suprachiasmatic nucleus (SCN), and projections to other hypothalamic nuclei and the pituitary.

Indeed, we find that the mass-dependency and mass-independency of life history relationships with RI periodicity align with hypothalamic-mediated neurosecretory anterior and posterior pituitary outputs. Anterior pituitary outputs are consistent with controls over all mass-dependent life history characteristics and metabolism, whereas posterior pituitary outputs are consistent with the singular mass-independent characteristic, estrous cycle length. We suggest that the coordination of energy metabolism and body mass via SCN-integrated hypothalamic nuclei (e.g., the arcuate nucleus) is key for generating the HHO and for establishing an integrated life history matrix.

We propose two models for understanding how the mechanics of long-period oscillations might behave, which are based on the premise that RI and HHO are the product of a sinusoidal rise and fall of metabolism. In Model 1 we assume that metabolic rate fluctuates periodically, while in Model 2, we assume that metabolic rate does not oscillate. If we see an oscillation in BMR in adult animals, then Model 1 is probably right. If there is no BMR oscillation in adult animals, then Model 2 is likely more correct (our preference), and we should, for instance, be able to see stepwise changes in metabolic rate in growing animals along with high-resolution metabolite variation due to SMR resource allocations.

The HHO represents a novel biological timing mechanism that modulates an SCN-integrated set of hypothalamic nuclei, thus the proximate objects of selection for body size and life history variability ultimately trace to variations in hypothalamic function, but may also include projections to (e.g., brainstem) and from the hypothalamus (e.g., pituitary). Evolution of the HHO is suggested to arise from selection operating on body mass. For instance, density dependent extrinsic mortality selects for age at sexual maturity, but it does so by modifying HHO regulation of body mass.

We have established the hypothesis that the HHO regulates primate life history by means of body mass-dependent, mass-independent, and metabolic rate variation, and that body mass, reproduction, and metabolism are centrally linked to the HHO, which acts as a mediating mechanism in the regulation of life history according to metabolic constraints. In conclusion, we provide evidence of long period biological timing, which represents a centrally regulated and oscillating adjustable long-period rhythm responsible for many aspects of organismal behavior, metabolism, and life history.

2. Introduction to life history of mammals

Life history is one of the most integrative fields of study in biology, which concerns the pace and pattern of life. The life history of mammals is typically described by the following characteristics: female and male body weight (body mass), gestation length, weight of individual neonates (birth weight), number of offspring per litter, weaning age (lactation length), estrous cycle length, age of first breeding for females, age at sexual maturity for females and males, maximum recorded lifespan (lifespan), interbirth interval, neonatal brain weight, and adult brain weight (endocranial volume) (Harvey and Clutton-Brock, 1985), in that order.

Harvey and Clutton-Brock (1985) consider each a life history variable, but these characteristics can be grouped into two classes. One group relates to the timing and duration of life stages (i.e., gestation length, lactation length, estrous cycle length, age of first breeding, age at sexual maturity, lifespan, and interbirth interval), profoundly shaping a species' reproductive efficacy. Body and organ masses are also included in compendia of mammalian life history characteristics because body size is fundamental to an organism's physiology and metabolic ecology (i.e., body mass, birth weight, number of offspring per litter, neonatal brain weight, and adult brain weight (endocranial volume). While co-varying with variables describing life schedules, mass characteristics are not themselves life history variables per se (e.g., Robson and Wood, 2008), but represent outcomes of developmental timing. For instance, given constraints on primate fetal growth rate trajectories, gestation length is highly correlated with birth weight (Harvey and Clutton-Brock, 1985). By the same token, age at completion of the dentition (a measure of the timing of skeletal maturity) is highly correlated with adult body mass (Smith, 1989).

The coupling of developmental timing with mass characteristics renders a life history matrix packaged so tightly together that no one trait appears free to vary without corresponding relative changes in the others (Charnov, 1991; Harvey and Clutton-Brock, 1985; Harvey and Nee, 1991; Smith, 1989). While the physiology of most life history traits and mass characteristics are well characterized, the factor(s) regulating the *combination* of traits that define the overall life history matrix of a mammal are completely unknown. However, to

understand how a life history is achieved would have considerable impact on fields of biology, ecology, anthropology, medicine, and behavior, and contribute, for example, to insights relating to the life of a single person or to the nature of how the lives of humans are patterned in comparison to the lives of other species.

Metabolism is responsible for energy allocations that fuel all aspects of life history, exerting primary control over the pace and pattern of life (Brown et al., 2004). Moreover, as all life history traits and mass characteristics reflect dependence on rate and time, it follows that metabolic rate must be inextricably linked to a biological timing mechanism. At small time scales, the daily biological, or circadian clock in mammals (and most other organisms) is observed to regulate metabolism and to apportion energy for the building, functioning, and maintaining of the body (Asher and Schibler, 2011; Bass and Takahashi, 2010; Gimble et al., 2011; Kalsbeek et al., 2011; Rudic et al., 2004; Schibler and Sassone-Corsi, 2002; Turek et al., 2005). However, while the circadian clock may at first glance appear key for establishing life history, it has been impossible to link these daily oscillations, which are held in common by all mammals, to the enormous life history variation expressed by the class. We reduce this problem to an examination of two kinds of time: external time (e.g., daily astronomical variation) and biological time (e.g., development schedules). Our principal questions are, "how can biological time be integrated to external time", and "how can biological time be varied to produce the enormous life history variation we observe"? Because timing is fundamental to establishing life history, we speculate that a longer period biological clock regulates variability of the pace and pattern of life, which predictably varies with life history strategy. Evidence that such a long period clock exists has recently emerged from an unlikely place, the skeleton.

3. Background to enamel

It has long been observed that mammalian tooth enamel (and also dentine) contains periodic "signals" in its microscopic anatomy, which are laid down as increments within a mineralizing matrix during the formation of the tissue. These signals attribute to both daily and long period secretion rhythms (Asper, 1916; Boyde, 1964; Dean, 1987). Enamel-forming cells, the ameloblasts, secrete their matrix with a circadian periodicity (Boyde, 1989; Bromage, 1991; Lacruz et al., in press; Mimura, 1939; Okada, 1943), giving rise to increments referred to as cross striations, or alternating varicosities and constrictions, which are observed by a variety of microscopy techniques and widely used in studies of primate dental development and life history (Boyde, 1989; Bromage and Dean, 1985; Dean, 1987; Smith, 2006) (Fig. 1). Studies have shown that there are also longer period enamel formation rhythms, which form incremental lines known as the striae of Retzius (Retzius, 1837) that represent a temporary but profound periodic slowing of enamel formation in multiples of whole days (Boyde, 1989; Dean, 1987; Fitzgerald, 1998; Shinoda, 1984; Smith, 2006) (Fig. 1). In many mammal species striae of Retzius also present on lateral enamel crown surfaces as imbricational features called perikymata. In respect to tooth root dentine, in the same manner, incremental structures representing the long period rhythm appear as Andresen lines, which express at the surface as periradicular bands (Bradford, 1967; Smith and Reid, 2009). The number of daily increments between adjacent striae of Retzius is called the repeat interval (RI), which is identical for all teeth of an individual but is variable between and sometimes within species (Fitzgerald, 1998).

Cross striations are the result of a daily variation in ameloblast secretory rate and mineralization chemistry (Boyde, 1989; Lacruz et al., in press), but the etiology of striae of Retzius is unknown despite the exceedingly periodic nature of their expression. However, it has been shown that the repeat interval enigmatically correlates with one of the most fundamental of mammalian biological traits, body mass (Bromage et al., 2009; Dean and Scandrett, 1995; Hogg, 2010; Smith, 2008) smaller-bodied species have short repeat intervals, while those of larger-bodied species are longer. It has also emerged that the duration of an animal's repeat interval in enamel is that same period required for bone forming cells, the osteoblasts, to form one increment of bone, the lamella (Bromage et al., 2009); it is not unreasonable to assume that growth increments in bone would show a relationship with body mass, insofar as the scaling of bone mass to body mass is an axiom of vertebrate hard tissue biology (Schmidt-Nielsen, 1984). We termed this period the "Havers-Halberg Oscillation" (HHO; (Bromage et al., 2009), in reference to Havers (1691), the first to observe and describe both the lamellae in bone and the striae of Retzius in enamel, and Franz Halberg, a long-time explorer of long-period rhythms (Halberg et al., 1965; Halberg et al., 2004).

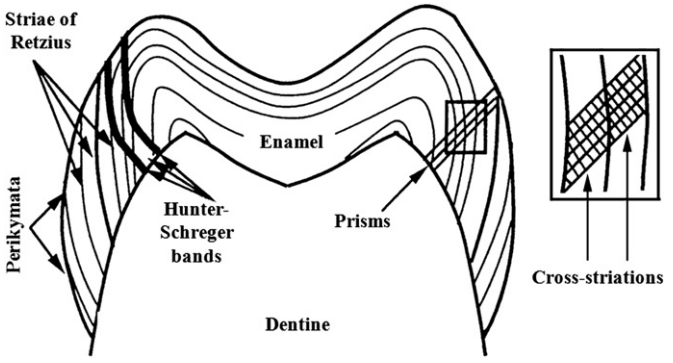

Fig. 1. A human molar crown is represented in cross section. Enamel forming cells develop prisms that course from the inner border of dentine to the outer surface enamel. Striae of Retzius are growth lines, each of which represents the instantaneous growth front of all enamel prisms developing at that increment. Between adjacent striae of Retzius are the daily cross striations, the number of which is called the repeat interval. During enamel formation, other microanatomical characteristics appear, such as perikymata, which are the surface manifestations of striae of Retzius, and Hunter-Schreger bands that relate to prism orientation variation. Figure adapted from Rozzi et al. (1999).

The mathematical basis for examining relationships between characteristics of an organism and body size was formulated by Huxley (1932). The so-called "heterogonic" equation, later renamed "allometric" (Huxley and Tessier, 1936), is a power function for relating a dependent variable, such as organ size, to an independent variable, such as body size. Huxley's contribution to the field of analytical morphology dealt largely with the biological understanding of proportionate growth. Correlation and regression statistics used by him continue to be the primary means for analyzing how life history attributes vary predictably with body mass (Calder, 1996), which enjoy good statistical support (Stumpf and Porter, 2012). In the present study, we use these methods to analyze the degrees of relationship between long period rhythms and life history traits and metabolic rates in the order primates.

4. Material and statistical methods

Values for primate RI were taken from Bromage et al. (2009), which vary from RI=1 (i.e., RI equals one day) for the smallest bodied primates to RI=11 for the largest bodied primate. RI were compared statistically to the commonly studied life history traits and mass characteristics, which, in the order presented by Harvey and Clutton-Brock (1985), include female and male body mass (kg), estrous cycle length (d), birth weight (gm), gestation length

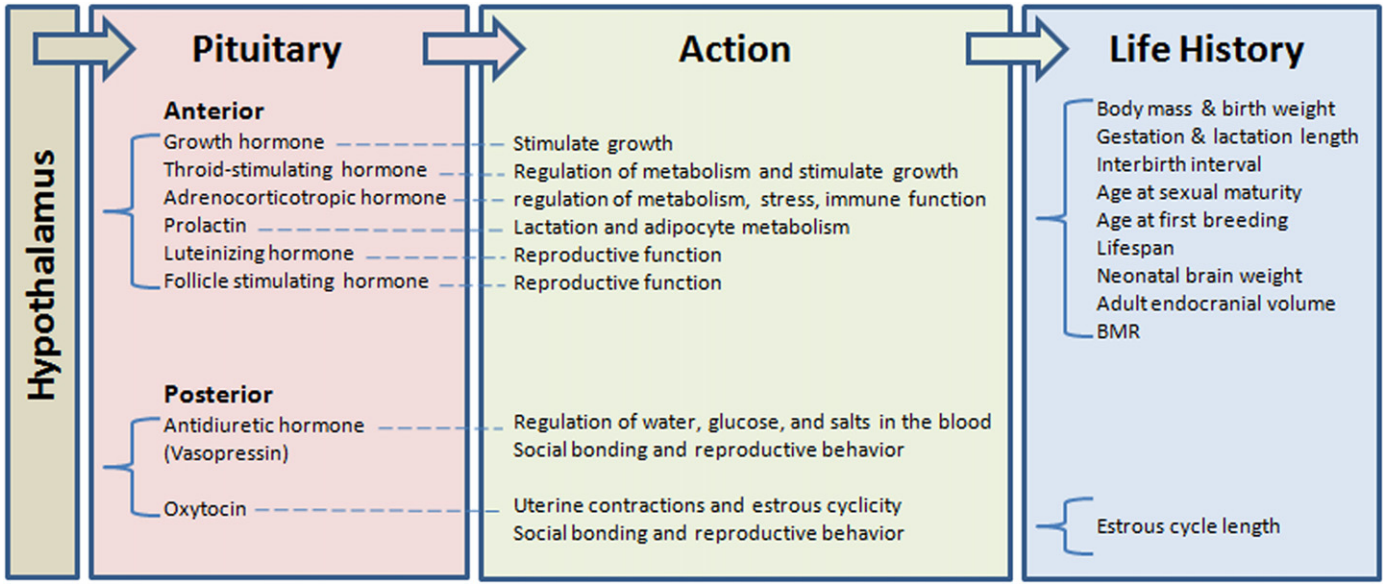

Fig. 2. Hypothalamic signaling stimulates pituitary secretions that in turn act on endocrine glands that result in a variety of physiological actions. The hypothalamic-pituitary axes are hypothesized to separate mass-dependent life history traits and BMR through the anterior pituitary and mass-independent estrous cyclicity and blood pressure through the posterior pituitary.

(d), lactation length (mo), interbirth interval (d), age at sexual maturity for females (mo), age of first breeding for females (mo), lifespan (yr), neonatal brain weight (gm), and adult endocranial volume (cc) for primates generally and for the hominin lineage. Raw data concerning the relationship between RI and body mass are provided in Appendix A (Supplementary online material), Table A1. Table A2 provides the raw data for RI in relation to all other life history traits and mass characteristics except endocranial volume, which may be found in Table A3 (non-human primate) and Table A4 (hominin).

RI was also statistically compared to primate basal metabolic rate (BMR) in Watts (Table A5) (Isler et al., 2008; Savage et al., 2004) and specific metabolic rate (SMR) in Kcal/g of body mass per day (Table A6) (Tolmasoff et al., 1980). To confirm that primate SMR reflects tissue-specificity, SMR in Kcal/g of body mass per day was regressed against osteocyte lacuna density for primates (Table A6) (Bromage et al., 2009; Tolmasoff et al., 1980), which represents the cell population contained within bone tissue.

The summary statistics describing the associations between RI and life history traits, mass characteristics, and metabolic rates and between all covariates are presented as correlation matrices (Tables A7 and A8).

Because RI has previously been shown to significantly relate to body mass, our interest also lay in describing the extent to which RI would remain associated with the other variables when controlling for body mass by performing several statistical tests, each of which use the same underlying arithmetic. A partial correlation matrix of RI against life history traits, mass characteristics, and metabolic rates were constructed with body mass as the control variable to remove the RI-dependent effects of body mass (Table 2 and Table A9). We also took the residuals arising from the regression of primate RI against body mass and regressed them against life history traits, mass characteristics, and metabolic rates (Table A10). In addition, expectations were that a stepwise multiple regression of RI against body mass as a predictor variable, would include additional predictors as suggested by the tests of residuals above (Table A11).

RI was log ($\log_{10}$) transformed on all regressions. Most, if not all, life history traits scale allometrically with body mass, i.e., they can be expressed as a power law of mass: $Y=aX^b$. After log-transformation, we have $\mathrm{Log}Y=b\mathrm{Log}X+\mathrm{Log}a$. When we perform a linear regression of Log(Y) on Log(X), we can obtain the slope b, which is the scaling power. Most life history traits associate together by allometric scaling laws, because they have been observed to scale with body mass. Thus, to find the scaling power, we must log-transform RI.

All statistics were performed using SPSS Statistics 17.0 (IBM Corporation, New York). Linear regressions were executed using the Least Squares Model and reporting the Pearson product-moment correlation coefficient (r) and its statistical significance (p), and the adjusted coefficient of determination (R^2). Correlation and partial correlation reporting included r, p, and either the number of pairwise cases (N, in the case of correlation) or degrees of freedom (df, in the case of partial correlation). A relationship was considered significant when $p \leq 0.050$.

5. Results

Correlations between RI against eleven life history and mass variables, BMR, SMR and between SMR and osteocyte density and summary statistics are reported in Table 1; correlation matrices are provided in Tables A7 and A8. The correlations with RI for ten of the variables are positive, high, and significant; only the association of RI with estrous cycle length is not statistically supported. Because RI=1 primates consistently group to the right side of a best fit line (graphics not shown), tipping the slope of the relationship upward, we repeated the correlations excluding these taxa. Results show that without these taxa the slope is consistently reduced in all tests (Table 1), suggesting that an explanation for the RI=1 primate life history adaptation is needed. Most intercorrelations are high and significant, the major exceptions being correlations between estrous cycle length and other variables and between SMR and life history traits and mass characteristics (Tables A7 and A8).

RI was significantly correlated with primate BMR, and correlated more so when the hypometabolic orangutan (*Pongo*) was removed from the data set. RI was not correlated with SMR when all taxa were considered, but when removing *Pongo*, as above, and

Table 1
Summary statistics of the log–log regressions of RI with life history traits and metabolic rate, and of metabolic rate with osteocyte lacunae density. In all tests of association between RI and primate life history traits, regressions were performed with (w/) and without (w/o) RI=1 taxa if present in the data set. In the test of association between RI and BMR, an additional test was made without the hypometabolic *Pongo*. In the test of association between RI and SMR, an additional test was made without the hypometabolic *Pongo* and *P. anubis*. See Discussion.

Tests of association	Regression variation	*r* value	*p* value	R^2 value (adjusted)	Slope
RI vs Body mass (kg)	w/RI=1	0.899	<0.001	0.802	0.304
	w/o RI=1	0.927	<0.001	0.853	0.246
RI vs Estrous cycle length (days)	w/RI=1	0.453	=0.120	0.133	1.091
	w/o RI=1	0.014	=0.968	−0.111	0.025
RI vs Birth weight (g)	w/RI=1	0.916	<0.001	0.831	0.412
	w/o RI=1	0.919	<0.001	0.835	0.334
RI vs Gestation length (days)	w/RI=1	0.692	=0.001	0.451	2.214
	w/o RI=1	0.646	=0.004	0.381	1.383
RI vs Lactation length (days)	w/RI=1	0.855	<0.001	0.718	0.582
	w/o RI=1	0.860	<0.001	0.725	0.436
RI vs Interbith interval (days)	w/RI=1	0.804	<0.001	0.625	0.763
	w/o RI=1	0.776	=0.001	0.572	0.526
RI vs Age at sexual maturity (months)	w/RI=1	0.787	=0.001	0.584	0.667
	w/o RI=1	0.771	=0.006	0.549	0.381
RI vs Age at first breeding (months)	w/RI=1	0.809	<0.001	0.630	0.729
	w/o RI=1	0.800	=0.001	0.609	0.530
RI vs Lifespan (years)	w/RI=1	0.918	<0.001	0,831	1.228
	w/o RI=1	0.877	<0.001	0.747	0.902
RI vs Neonatal brain weight (g)	w/RI=1	0.897	<0.001	0.785	0.433
	w/o RI=1	0.902	<0.001	0.791	0.314
RI vs Adult endocranial volume (cc)	w/RI=1	0.875	<0.001	0.760	0.390
	w/o RI=1	0.887	<0.001	0.781	0.327
RI vs Hominin endocranial volume (cc)		0.943	<0.001	0.871	0.255
RI vs BMR (Watts)[c]	w/*Pongo*	0.876	<0.001	0.746	0.454
	w/o RI=1 & *Pongo*	0.937	<0.001	0.862	0.286
RI vs SMR (Kcal vs g)	all taxa	0.456	=0.364	0.009	−0.535
	w/o *Pongo & P. anubis*	0.977	=0. 023	0.931	−1.460
SMR (Kcal vs g) vs Osteocyte lacuna density		0.943	<0.016	0.852	1.083

P. anubis, the relationship is supported; the body weight of *P. anubis* used to assess SMR was 22% higher than the specimen used to obtain RI, skewing the data set. Finally, SMR was found to be significantly correlated with osteocyte density.

With body mass employed as the control variable, partial correlation was performed between RI and life history traits, mass characteristics, and metabolic rate variables. RI failed to significantly associate with any life history trait except lifespan, and then only weakly, or with any mass variable when all primates were included in the analysis (Table A9). RI was highly and negatively related to SMR, though the sample size is small. However, when RI=1 primates were excluded from the analysis, the association that RI has with estrous cycle length was found to be high and significant ($r=1.0$, $p<0.001$; Table 2). The same high relationship and significance is exhibited by the association between RI and SMR, acknowledging again the small sample size. After controlling for body mass, less than half of the intercorrelations were significant (Tables A2 and A9).

Because the same underlying arithmetic is employed, the results of partial correlation should be consistent with the results of tests of body size adjusted residuals and stepwise multiple regression. Residuals calculated from regressing RI against body mass were used in regressions against the other life history traits, mass characteristics, BMR, and SMR to test for the RI-dependent effects of body mass on the associations that RI has with these variables. Consistent with summary statistics reported in Table 1, residuals were calculated with and without RI=1 species, using the raw data provided in Tables A1–A6, and summarized in Table A10. Linear regressions of the residuals failed to reveal any significant linear or non-linear association with life history, mass, BMR, or SMR (SMR is acknowledged to have very few data points). However, when RI=1 primates were removed from the analysis, estrous cycle length alone was significantly and positively associated with RI adjusted body size residuals.

Stepwise multiple regression was performed in tandem with tests of partial correlation and residuals against life history traits, mass characteristics, and metabolic rates (Table A11). Of all study variables, only body mass was significantly and highly associated with RI when all primates were included, and only estrous cycle length contributed to the association with RI when RI=1 primates were excluded from the analysis.

6. Discussion

Biological rhythms exert considerable regulatory control over an organism's physiology, behavior, and development, which are particularly visible as daily metabolic fluctuations attributable to the central circadian clock (Nagai and Nakagawa, 1992). Dental hard tissues reflect these cycles, but also provide longer periodic signatures such as RI, occurring in multiples of whole days (Fig. 1), which offer a unique window into the study of long period timing in relation to organismal life history.

Previously we reported a high, positive, and significant statistical association between RI and body mass among primates and other mammals (Bromage et al., 2009). The primate relationship regresses with slope 0.304 (0.246 when RI=1 taxa are removed), which is very near the expected 0.25 slope found for a variety of mass-dependent lengths of biological periods/cycles – ranging from muscle contraction time to lifespan – regressed against body mass (Lindstedt and Calder, 1981).

To test the broader applicability of associations that RI has with primate life history, regressions of RI were performed against most other common life history traits and mass characteristics. While much primate life history data may be gleaned from the literature, there remain limitations in the numbers of species for which both RI and life history information is available. However, samples are now sufficient to reveal in all cases but

Table 2
Partial correlation matrix of primate striae of Retzius repeat intervals (RI) against life history traits and metabolic rate whilst controlling for body mass (all primates except those with RI=1 were used). Significant correlations are bold.

Variable														
Control	Variable		**1**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
2 Body mass	**1** RI	*r*													
		p													
		df													
	3 Estrous length	*r*	**−1.000**												
		p	**.000**												
		df	**8**												
	4 Birth weight	*r*	.156	−.322											
		p	.524	.307											
		df	17	10											
	5 Gestation length	*r*	−.480	.424	.366										
		p	.051	.169	.136										
		df	15	10	16										
	6 Lactation length	*r*	−.006	−.255	.410	.412									
		p	.982	.449	.082	.090									
		df	16	9	17	16									
	7 Interbirth interval	*r*	−.242	.394	**.533**	**.698**	**.723**								
		p	.405	.261	.033	.003	.002								
		df	12	8	14	14	14								
	8 Age at sexual maturity	*r*	−.402	.406	**.737**	**.614**	.380	**.797**							
		p	.249	.319	.010	.044	.223	.003							
		df	8	6	9	9	10	9							
	9 Age at first breeding	*r*	−.116	.514	**.673**	**.667**	.482	**.798**	**.906**						
		p	.706	.157	.008	.009	.081	.001	.000						
		df	11	7	12	12	12	12	8						
	10 Lifespan	*r*	.177	−.032	**.753**	.323	.463	**.702**	**.893**	.531					
		p	.602	.935	.005	.261	.111	.016	.003	.093					
		df	9	7	10	12	11	9	6	9					
	11 Neonatal brain weight	*r*	−.042	−.619	**.730**	.584	.245	.512	.659	**1.000**	**.893**				
		p	.914	.076	.011	.077	.496	.159	.054	.000	.003				
		df	7	7	9	8	8	7	7	6	6				
	12 Adult endocranial volume	*r*	−.151	−.096	**.689**	.260	.167	.446	**.706**	**.596**	**.682**	**.859**			
		p	.471	.767	.001	.283	.481	.083	.010	.019	.007	.001			
		df	23	10	19	17	18	14	10	13	12	9			
	13 BMR (W)	*r*	.122	**.849**	**.742**	**.706**	.177	**1.000**	**1.000**	**.754**	**.896**	.472	.528		
		p	.755	.016	.014	.015	.602	.000	.000	.019	.001	.344	.095		
		df	7	5	8	9	9	9	5	7	7	4	9		
	14 SMR (KCAL)	*r*	**1.000**	**1.000**	−.064	−.193	.349	−.356	**1.000**	**1.000**	**1.000**	**1.000**	.335	.	
		p	**.000**	.000	.936	.807	.651	.644	.000	.000	.000	.000	.665	.	
		df	**2**	2	2	2	2	2	1	1	1	1	2	0	

one – estrous cycle length – that statistical associations are high, positive, and significant (Table 1) with the variables. In earlier work, estrous cycle length was also singled out as being non-significantly related to other life history traits (Harvey and Clutton-Brock, 1985). We will return to this conundrum below.

To understand the effects of body mass on these statistical associations, we performed several tests. In the first, partial correlation employing body mass as the control variable confirmed that RI associations with the other life history traits – excepting estrous cycle length – and mass characteristics are due to the dependence of RI on body size (Tables A2 and A9), and when RI=1 primates are removed, the relationship between RI and estrous cycle length is significant and represented by $r=-1.0$ (SMR is also highly correlated, but we acknowledge the small sample sizes).

In a second test of the influence of body mass on associations with RI, the residuals of RI regressed against body mass were subsequently regressed back against body mass and found to be randomly distributed (Table A10). This suggests that there is a simple linear relationship between RI and body mass. The dependence of RI on body mass would further suggest that these RI residuals ought also to be randomly distributed against other life history traits, mass characteristics, and metabolic rates if they were largely dependent upon body size; a perusal of the results of these tests summarized in Table A10 demonstrates this to be the case. The relationship between RI residuals and estrous cycle length, however, is significant for RI ≥ 2 taxa. A visualization of the data (graphic not shown) suggests that as estrous length increases, variability of the residuals decreases.

Finally, stepwise multiple regression demonstrated that the singularly most significant relationship is that between RI and body mass. However, of all other life history traits, mass characteristics, and metabolic rates, only estrous cycle length was an additional significant predictor in the model (Table A11).

These results suggest that the oscillation represented by RI exerts overarching control of organismal life history by means of its regulation of body mass. Estrous cycle length remains a curious outlier in all tests that exclude RI=1 primates.

6.1. *The significance of RI=1*

Our attention is repeatedly drawn to the offset of RI=1 primates from all other RI ≥ 2 primates in tests of RI associations with the variables employed. RI=1 primates have relatively larger bodies and brains and longer gestation and lactation lengths, etc., than expected for their RI, and removing them from the statistical analyses decreases slopes of all regressions. Strictly speaking, we do not know if the daily increments of enamel in RI=1 primates are formed on the physiological foundation responsible for the classical circadian oscillation or of mechanisms responsible for

striae of Retzius, should a difference exist between the two. But one thing is clear, RI=1 primates keep to ca 24-hour timing; a long period enamel rhythm is not present in these animals as far as we have been able to discern. RI=1 primates thus present an interesting dilemma. Nevertheless, because a day is one turn of the Earth for both a small and large bodied mammal, circadian rhythms per se are unlikely to be directly related to the scale of animal life (Smith, 1992), and because of this, circadian timing cannot completely explain the evolution of allochronic relationships.

The grouping of RI=1 primates to the right of the best fit line nevertheless illustrates something important about the origins of primate life history scaling. Relative to their body mass, primate production energy is surprisingly low, at about 40% of that of other mammals (Charnov and Berrigan, 1993). This means that primates take longer to gestate, longer to wean, longer to reach their adult body and brain sizes, and live longer, etc., relative to non-primate mammals of the same body mass, which tells us that selection for the novel primate life history matrix occurred within the constraints of their ca. 24 h rhythmicity; precociality vs altriciality, mode of placentation, resource allocations to reproduction and growth, etc. were modified to generate a life history strategy tuned to the pace and pattern of primate life. For instance, the gestation times of altricial mammals are known to be relatively short compared to precocial mammals. The rat has a body mass similar to that of the primate *Callithrix pygmaea*, and both have an RI of 1, yet gestation lengths are 22 and 137 days, respectively. However, we suggest that to evolve the full spectrum of primate life that characterizes the order primates, at all body masses, taxa evolved variability in the oscillation responsible for RI as a biological timing mechanism by which life histories are regulated (i.e., the HHO).

If RI is to be useful in explaining life history evolution, then an explanation for life history transformations from RI=1 is necessary. We argue that to evolve the full spectrum of primate life that characterizes the order today, taxa evolved HHO variability as the biological timing mechanism by which life histories are regulated at larger body masses. It is intuitive to consider that RI=1 represents classical circadian timing, in that a long period rhythm is not present in these animals. However, based on our current understanding, it cannot be said whether HHO and RI are under strictly circadian regulation under central control by the suprachiasmatic nucleus (SCN) of the hypothalamus, or whether it operates on a separate clock; there are suggestions of multiple circadian oscillators present in the SCN, and of a central clock residing outside the SCN (Nagai and Nakagawa, 1992). Another possible explanation is that a unique physiological clock exists, which is primitive to all mammals (and possibly even tetrapods/vertebrates), which is inherently variable in periodicity, and is represented by RI. The biology of this clock may have undergone changes in physiology at RI=1 (i.e., primitive, small body masses) in different mammalian lineages, generating life-history scaling relationships that continue to be unique features of specific taxa such as the primates.

Either way, due to the small sizes of primitive mammals, we suspect that many ordinal level mammalian life history matrices were formulated at RI=1 stages of their evolution, after which long period HHO rhythms evolved in response to selection pressures to increase life history, mass, and metabolic variation within some orders. A concomitant of increased mammalian life history variation is the requirement to make body mass-dependent adaptive adjustments to density dependent juvenile mortality patterns (Charnov, 1991). For instance, reduced juvenile mortality at small adult body mass (i.e., RI=1) is a consequence of enhanced primate maternal care, which is a necessary concomitant of species having reduced production energy. Further reductions in juvenile mortality may occur with selection for larger adult (and thus also neonatal) body mass and extending the length of care of larger juveniles, which we suggest is causally related to selection for variation in HHO and adjustments to the life history matrix (see Section 8 for a discussion of proximate objects of selection).

6.2. Covariation of life history traits

Having previously established a statistical association between RI and body mass (Bromage et al., 2009), the associations of RI with life history traits and mass characteristics reported above is not surprising given the high degree of covariation between traits of the life history matrix (Charnov, 1991; Harvey and Clutton-Brock, 1985; Smith, 1989), which is evident in Tables A7 and A8.

> "Such covariation 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" (Harvey and Nee, 1991).

RI is a response to an oscillation postulated by us to regulate body mass, and through this relationship, much of the life history matrix. As such, we regard the HHO as a candidate for consideration as a "key variable". Previously the concept of "physiological time" has been proposed, which is said to be a biological time scale that varies predictably between organisms (Brody, 1945) and hypothesized to entrain a body mass-dependent clock (Hill, 1950). Biological times are suggested to scale according to this mass-dependency and regulate mammalian life history in ecological/metabolic context (Lindstedt and Calder, 1981; Lindstedt et al., 1986). HHO might conceivably relate to the mechanism responsible for the scaling of physiological time; i.e., an oscillation that powers and entrains this mass-dependent clock. Slopes of mass-dependent physiological timings typically express a slope of around 0.25 as noted by Calder (1996):

> It appears that the many biological events and cycles of events in the body occur as relatively constant multiples of one another and in times proportional to (body mass)$^{1/4}$. How are these scalings selected in the evolutionary process? Certainly if one function is designed in proportion to $M^{1/4}$, other functions tied to it will be affected by that scaling… (p. 151)

However, a fascinating deviation from expectations of tests of physiological time is the variety of slopes that characterize the relationships between RI and the study variables (Table 1). A similar heterogeneity of scaling relationships has been observed when primate life history traits and mass characteristics are regressed against age at eruption of the first permanent molar (Smith, 1989), which is a significant indicator of biological age. Because of energetic tradeoffs, it is conceivable that with the appropriate statistical technique, some life history characteristics may combine their scaling coefficients to establish quarter power scaling relationships. Nevertheless, the basis of RI biological timing is not physiological time in the classical sense; the HHO is adjustable. That RI variability adjusts to units of whole days, suggests a primary metabolic role for the circadian clock in its metric: It is axiomatic that "…the physiological time-scale of an animal has to compromise with the constant time-scale of the external world…" (Hill, 1950) (p. 227).

To investigate the relationship that RI has with metabolism, RI was regressed against BMR and found to be high, positive, and significant when the effects of body size remain tethered to RI. Orangutans (*Pongo*) are known for their hypometabolism, which is considered an adaptation to avoid protein imbalance during

periods of fruit scarcity (Vogel et al., 2011), and removing them (and RI=1 primates) from the association improves the correlation (Table 1). BMR (and birth weight) retains a significant interdependency with other study variables after correcting for body mass, only failing to be significantly associated with RI, neonatal brain weight, and adult endocranial volume (Tables A2 and A9). However, while samples are small, when controlling for both body mass and BMR, nearly all covariations between study variables disappear excepting those with estrous cycle length (Table A12). This suggests that whole body metabolic rate, combined with that of HHO-regulated body mass, is key for establishing life history variation.

Concerning an association between RI and SMR, a significant relationship was not borne out using all of the data available. However, to assess the veracity of this result, we removed the hypometabolic orangutan as well as *P. anubis*, whose SMR, it turns out, was calculated from an individual with body mass 22% higher than that of the specimen which provided the RI. When adjusting the data thusly, the association between RI and SMR became high, positive, and significant (Table 1). These results suggest that RI associates with both whole body metabolic rate (i.e., BMR) and with the metabolism of tissues (i.e., SMR) that make up that body. To confirm that primate SMR harbors tissue-specificity in its rate metric, SMR was regressed against primate osteocyte density, a proxy for bone tissue metabolism, and it was found that these two variables correlate highly and positively (Table 1).

6.3. Metabolic rate and cell proliferation

It is an axiom of vertebrate life history that whole-body BMR scales positively with body mass, and that SMR scales negatively with body mass; i.e., as body mass increases, BMR rises and SMR becomes more energy efficient (Schmidt-Nielsen, 1984). The former relationship is borne out in regressions of RI against BMR, scaling positively with allometric slopes of less than 1.0 (Table 1). The latter relationship is also borne out in the regression of SMR with osteocyte density, having an isometric slope (slope=1.083): Here the slope is positive, but that is only because osteocyte density is inversely related to body mass (Bromage et al., 2009), thus decreased specific metabolic rate associates with the lower osteocyte densities of larger primates (i.e., reflecting a negative relationship whereby lower SMR occurs at larger body mass).

What mechanisms enable increased SMR energy efficiency at larger body masses? Increased metabolic efficiency at larger body mass does not relate to having fewer cells, thus it must be concerned with the metabolic regime of individual cells. In a fast growing mammal, high rates of cell proliferation carry a high metabolic cost when compared to the fewer proliferating cells per unit tissue mass in a slower growing animal. Furthermore, reduced rates of cell division are observed to lower cellular metabolic rates (Savage et al., 2007). One reasonable hypothesis, which we will briefly explore here, is that HHO represents a metabolic rhythm, which by means of oscillating resource allocations, regulates rates of cell division and activities, generating not only the relationship between SMR and body mass, but also the pace and pattern of mammalian life history.

The metabolic rate of a multicellular organism is equal to the aggregate metabolisms of all cells from all its tissues and organs. This rate, which sums the energy necessary to acquire, convert, and allocate energy to growth, reproduction, and maintenance, sets energetic limits on biological activities and is widely understood to establish the pace and pattern of life history (Brown et al., 2004). Thus the postnatal ontogenetic growth of a small mammal is relatively fast because of its relatively high rate of tissue-specific cell proliferation, which establishes relatively high cellular metabolic rates and lifetime SMR in support of its frenetic life history. A large mammal grows relatively slowly because of decreased rates of tissue-specific cell proliferation, which establishes relatively low cellular metabolism and lifetime SMR in support of a slow life history.

Fast postnatal growth and high SMR are resolutely coupled with small body mass and low BMR because only this combination is energetically and ecologically supportable, and then, only supportable over short life histories (Calder, 1996; McNab, 2002). Long life histories are a consequence of slow postnatal growth and low SMR at large body mass and high BMR. It is reasonable to assume that the continuum of mammalian life histories is modulated by mechanisms responsible for generating RI, an HHO biological timing mechanism regulating rates of cell proliferation and, in so doing, the body mass and SMR and BMR profile of a mammal.

Dependence of the cell cycle upon the daily circadian clock in mammals is well established (Bjarnason and Jordan, 2000; Matsuo et al., 2003; Miller et al., 2007; Nagoshi et al., 2004; Panda et al., 2002; Reppert and Weaver, 2002; Schibler, 2005; Ünsal-Kaç maz et al., 2005). This agrees with our expectations because this body of research is largely performed in the mouse, which is an RI=1 sized mammal, while those studies in human are undertaken on bone marrow, gut, oral mucosa, and cultured fibroblasts, which reflect tissue-specific dynamics of cell replacement and colonization (Koukkari and Sothern, 2006), not development. Such a research focus will miss fundamental long-period physiological rhythms regulating development. Having said this, however, should long-period cell proliferation rhythms exist, they would still manifest themselves through circadian clock machinery. We can expect that natural selection for increased body mass would use an already existing and elegant mechanism to regulate the frequency of cell proliferation and, as well, to allocate resources for growth to times of day when this is most efficient (Schibler, 2005), as would be particularly necessary for oscillatory increases in cell division.

For instance, an axiom of vertebrate biology is the relationship between bone mass and body mass (Schmidt-Nielsen, 1984). Bone mass is regulated by the proliferation rate of osteoblasts, the bone forming cell, which has been demonstrated in a small mammal to employ the molecular clock (Fu and Lee, 2003). Osteocyte lacuna densities, as they reflect the rate of osteoblast proliferation, transformation, and incorporation into bone as osteocytes during growth, are higher in mammals with rapid growth and small body mass, whose osteoblast proliferation rates lead to higher osteocyte lacuna densities. In larger bodied and slower growing mammals, the inverse is true, and osteocyte lacunae densities are lower (Bromage et al., 2009; Mullender, 1996). While the molecular clock regulates mass-dependent osteoblast cell proliferation, we suggest that the signal to employ this machinery operates on and derives from long period HHO biological timing.

When removed from their organismal context and placed in vitro, mammalian cells from different orders cease to scale their mass-dependent metabolic behaviors (Brown et al., 2007). This suggests that differences in SMR among species are the result of centralized organism-level control mechanisms as opposed to clocks in the periphery. It further suggests a hypothalamic origin for the HHO, likely to include in its pathway the mammalian centrally regulated circadian clock localized to the SCN, and projections to other hypothalamic nuclei, the pituitary, and the brainstem (see Section 6.4). For instance, one hypothalamic candidate for consideration is the arcuate nucleus, site of the melanocortin pathway. Pro-opiomelanocortin neuropeptides of the arcuate nucleus – α- and β-melanocyte-stimulating hormones – are primary regulators of energy homeostasis and body weight

(Biebermann et al., 2006; Lee et al., 2006). That lifetime specific metabolic energy expenditure is dependent upon body mass (see review by Speakman (2005)) is an indication that the coordination of energy metabolism and body mass via the arcuate nucleus is highly relevant to the establishing of an integrated life history matrix, a view also consistent with early research in metabolic ecology and organismal life history (Hennemann, 1983). Such coordination is consistent with the proposal that cell proliferation and rates of cell synthesis (e.g., matrix secretions) are manifestations of the HHO.

6.4. Hypothesized bioregulation of HHO

The vertebrate neuroendocrine system is composed of several hypothalamic-pituitary (HP) axes, which proximally include neurosecretory (hypophysiotropic) neurons within the hypothalamus, intermediate tropic hormone secreting cells of the pituitary gland, and distally targeted endocrine glands exhibiting a secretory response to their respective pituitary hormones (Norris, 2007). The anterior and posterior parts of the pituitary exhibit specific responses to hypothalamic stimuli. One category of hypothalamic outputs include releasing and inhibiting hormones that stimulate tropic hormone secretions from the anterior pituitary, which target the thyroid gland, gonads, adrenal gland, and liver, and that exhibit endocrine responses involved in the overall control of growth, metabolism, and reproduction (i.e., thyroid hormones, estrogen and progesterone, androgens, cortisol, and insulin like growth factors). The hypothalamus also synthesizes tropic hormones transported directly to the posterior pituitary, which, when secreted, regulate the uterus and kidneys in the control of estrous cyclicity, water balance, serum sugar and salt concentration, and social bonding and reproductive behaviors by oxytocin and vasopressin hormones. Moreover, the hypothalamus exerts direct nervous control of some peripheral endocrine-secreting cells, such as osteoblasts, via sympathetic innervation (Amling et al., 2001; Elefteriou et al., 2004; Karsenty, 2001; Lee et al., 2007; Takeda et al., 2003).

As a brief aside, the regulation of estrous cyclicity is commonly considered a function of anterior pituitary secretions of luteinizing and follicle stimulating hormones (LH and FSH, respectively) that regulate ovarian estrogen and progesterone levels in cycling mammals. However, the biological role of LH and FSH relate to the *growth and maintenance* of the uterine endometrium as a suitable implantation site for a fertilized egg. The regulation of estrous *cyclicity* is more complex and includes the hypothalamic hormone oxytocin, transported to and released from the posterior pituitary.

Hypothalamic controls of anterior pituitary hormones are generally those that we would consider important for most variables of the life history matrix and BMR, while hypothalamic control of posterior pituitary hormones relate to estrous cycle length and other functions (Fig. 2). This division of labor, we suggest, is mirrored in the Results herein (Section 4) and discussed in Sections 6 and 6.2, in which RI is described as significantly associated with life history traits through its association with body mass, with the exception of estrous length that, only when controlled for body mass, is also observed to strongly associate with RI. In hindsight, the result obtained for estrous cyclicity in relation to body mass may not be surprising. In deference to early research on human reproductive ecology (Frisch and Revelle, 1970), it is now well established that it is energy balance and not body mass that largely regulates ovarian function and estrous (Ellison, 1990).

In this model of HHO bioregulation, hypothalamic signaling to the anterior pituitary and direct sympathetic output control the life history traits of primates that are demonstrably RI-mass-dependent. These traits and BMR are well known to be regulated by the HP axis involving anterior pituitary secretions that fuel growth, development, and metabolism (Norris, 2007); lifespan may at first glance appear to be remote from this explanation, but rates of cell proliferation are indeed recognized to regulate longevity (Magalhães and Faragher, 2008). Hypothalamic regulation of the posterior pituitary controls that singular RI-mass-independent life history trait, estrous cycle length (in addition to water balance, blood osmolality, and blood pressure). Though some research implicates ovarian contributions of hormone in some species, posterior pituitary secretions of oxytocin have been long implicated in regulating estrous cyclicity (Falconer et al., 1980; Greer et al., 1986; Mitchell et al., 1982; Prince et al., 1995; Sarkar and Gibbs, 1984; Windle and Forsling, 1993). In passing, it is worth noting that reports of estrous-dependent blood pressure variability (Engel and Hildebrandt, 1974; Takezawa et al., 1994) suggest that estrous may be coupled to vasopressin secretions that also derive from the posterior pituitary.

Several hypothalamic neurosecretory nuclei project to the pituitary, which include the preoptic area, arcuate nuclues, supraoptic nucleus, paraventricular nucleus, and median eminence. Nestled among them is the SCN, site of the mammalian centrally regulated circadian clock (Weaver, 1998). Projections from the SCN to the rest of the hypothalamus are known to intersect each of these nuclei, rendering the conclusion that the SCN exerts influence over pituitary function (Nagai and Nakagawa, 1992).

Mammalian circadian "systems" include an input pathway connecting external synchronizers to a central clock (the SCN), whose oscillations regulate physiological processes (Koukkari and Sothern, 2006). However, whether the HHO has an input pathway or whether it is an endogenous oscillator (e.g., within a hypothalamic nucleus) independent of external synchronizers, exerting its effects through the SCN and/or other hypothalamic nuclei, is a question that remains for future research. Multiple ultradian, circadian, and seasonal rhythms are known to be represented as measurable variations in serum metabolites (see Koukkari and Sothern, 2006 for a brief review), and how we might go about their discovery is described below in Section 7.

7. Modeling long-period oscillations

To better understand how the mechanics of long-period oscillations might behave, we propose two models below. The models are based on the premise that RI and HHO are the product of a sinusoidal rise and fall of metabolism; at its zenith, cells might be performing their tissue-specific functions, while reserving cell proliferation rhythms to its nadir. For instance, osteoblast proliferation is regulated by the molecular clock (Fu and Lee, 2003), cell divisions taking place during a particular time of the day, while the remaining time in the period is dedicated to produce bone matrix (Gundberg et al., 1985; Simmons and Nichols, 1966).

We followed the model developed by West and colleagues (West et al., 2001), in which metabolic energy (rate) is partitioned between the energy allocated to maintenance of existing biomass, and energy allocated to synthesizing new biomass, i.e., $B = B_{\text{maint}} + \text{Growth}$. In West et al.'s model, B scales with body mass to a 3/4 power, as $B = B_0 m^{3/4}$, and B_{maint} is linearly proportional to body mass. So we have $dm/dt = am^{3/4} - bm$, where dm/dt is the growth rate, a and b are constants depending on the adult mass, M, and energy to synthesize one unit of biomass, and B_0, the normalization coefficient of the scaling law.

In Model 1 we assume that metabolic rate, B, fluctuates periodically as $B = am^{3/4}F[T(M),t]$, where $F(T,t)$ is a periodic function of time t, and T is the period, which in our case depends on the adult mass of the organism, M. We further assume that maintenance rate, B_{maint}, has the same period.

Thus, we have an equation

$$dm/dt = (1-c\sin[fM \times t])(am^{3/4}-bm) \quad (1)$$

In this equation we assume that $F(T)$ has the form, $1-c\sin(fM \times t)$.

The constant c determines the amplitude of the oscillation in B. The free parameter, f, can be determined by the relationship between RI and body mass, M. f has the dimension of $[1/(\text{mass} \times \text{time})]$.

Assuming adult mass is 55 g (like a mouse), we solved this equation for growth rate, $dm(t)/dt$ (Fig. 3), and metabolic rate (Fig. 4).

The growth rate reaches the maximum around day 10, and decreases to almost zero. We also plotted the difference between the non-oscillating curve and the oscillating curve, i.e., $m_{\text{non-osc}}(t)-m_{\text{osc}}(t)$ (Fig. 5).

There are two points we would like to raise concerning Fig. 5. First, the difference between the non-oscillating curve and the oscillating curve reaches the maximum when the growth rate reaches the maximum, i.e., day 10. Second, the maximum difference is too small in comparison to the adult mass. Thus the oscillation is not easy to see in the growth curve $m(t)$.

Additional parameters are required. In the model of West and colleagues (West et al., 2001) there is no free-adjustable parameter. The constants, a and b, are fixed for any given species, and it is claimed that they can be calculated from first principles. In our extended Model 1 we have two additional parameters, c and f. Parameter c determines the magnitude of the oscillation in metabolic rate (and mass curve), and f determines the period of the oscillation. Parameter f can be obtained from the data on the relationship between RI and body mass, M (this value can be double-checked from the data on metabolic rate). We suppose that there is no first principle on which we can derive c. In principle, both c and d can be measured empirically, if one observes an oscillation in metabolic rate.

The model presented above is a zeroth-order approximation; long term metabolic data is expected to facilitate more fine-tuning.

Alternatively, in Model 2, we assume that metabolic rate does not oscillate. Instead, the amount of energy allocated to growth and maintenance oscillates in the manner of $1-c\sin(fM \times t)$, and the growth equation becomes $(1-c\sin[fM \times t])dm/dt = am^{3/4}-bm$.

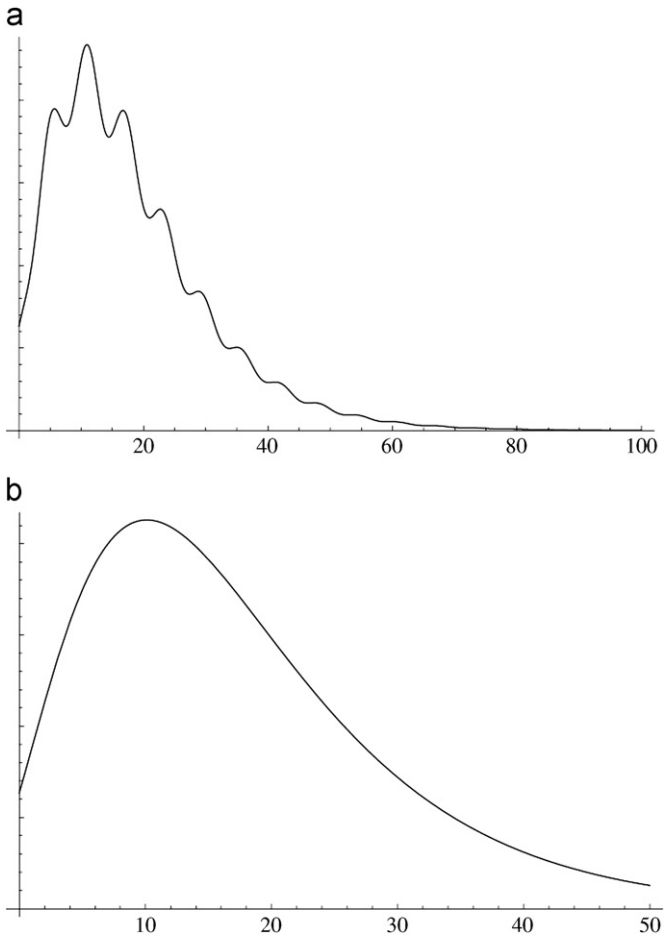

Fig. 3. Growth rate, dm/dt: (a) Oscillation; (b) no oscillation. The horizontal axis is age, t.

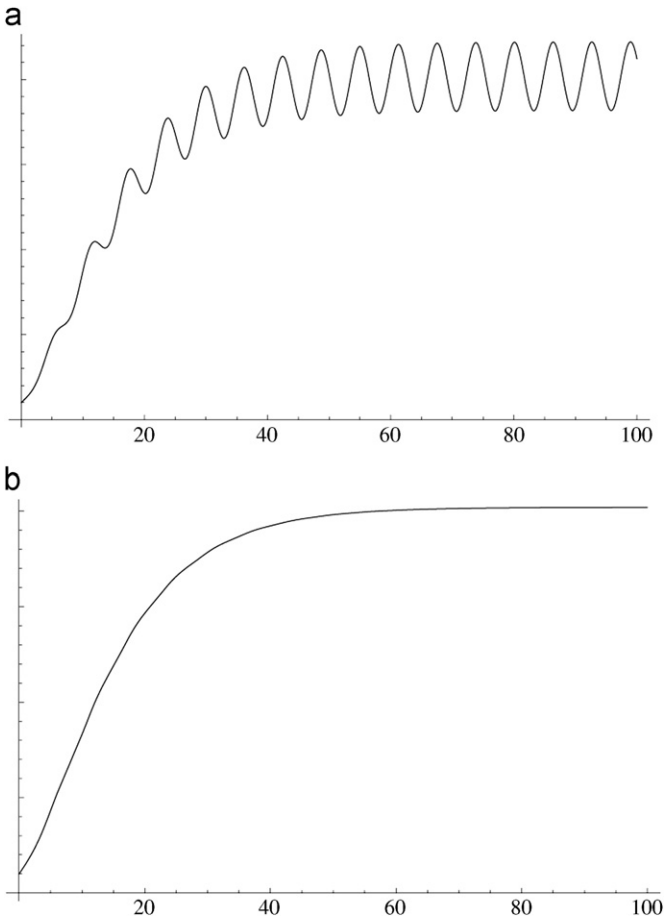

Fig. 4. Metabolic rate as a function of time: (a) Oscillation; (b) no oscillation. The horizontal axis is age, t.

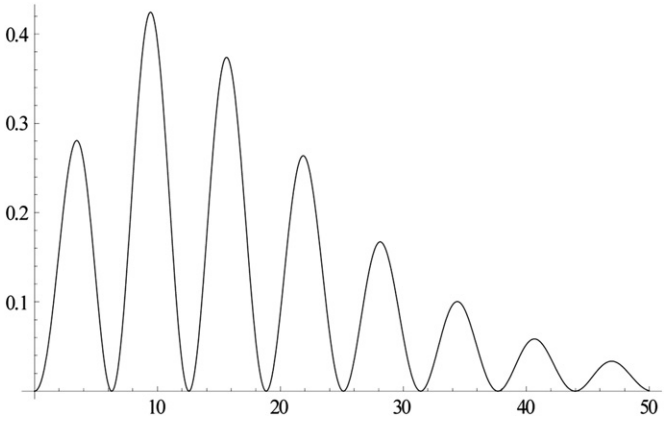

Fig. 5. The difference in growth rate with oscillation and without oscillation. The horizontal axis is age, t.

Mathematically, this equation is similar to Eq. (1), except that the oscillation term in Eq. (1) is on the right hand side. But biologically, the second model does not require the metabolic rate and maintenance rate to oscillate. The periodic growth revealed in enamel, RI, is attributed to the oscillation in energy supply to fuel growth (i.e., to support cell function on the one hand, and cell proliferation on the other).

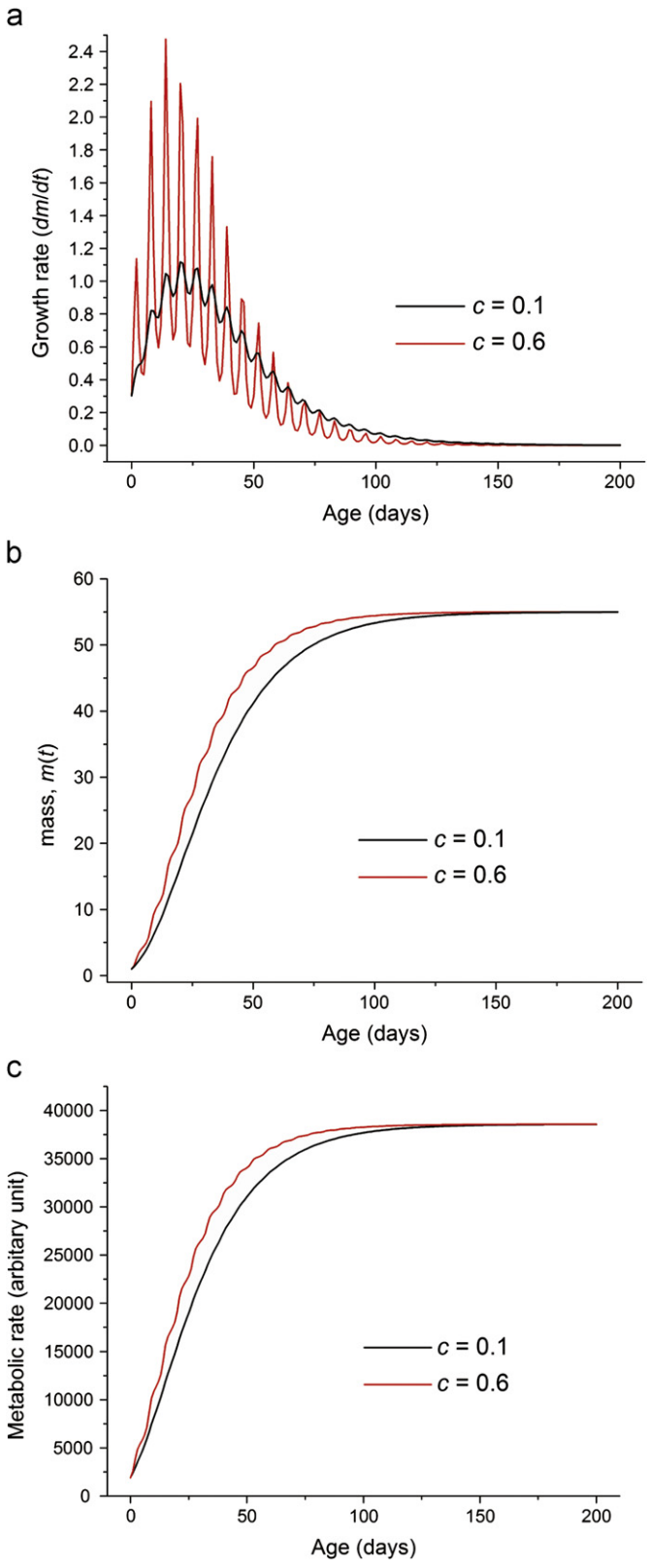

Fig. 6. (a) Growth rate, (b) growth curve, and (c) metabolic rate, each as a function of age.

In Fig. 6, we plot the growth rate, $dm(t)/dt$ (Fig. 6(a)), the growth curve, $m(t)$ (Fig. 6(b)), and the metabolic rate, $am(t)^{3/4}$ (Fig. 6(c)) as functions of age with the different constant, c ($=0.1$, and 0.6). The magnitude of oscillation in growth rate depends on the constant, c (Fig. 6(a)). Due to this oscillation, we see the periodic growth spurts in the curves, $m(t)$, which are more obvious when $c=0.6$. Since the growth finally ceases, i.e., $dm/dt=0$, spurts in the growth curve attenuate, and the curve becomes smooth after the adult mass is reached. In this model, we assume that metabolic rate is a function of mass, as $am^{3/4}$, so when mass, $m(t)$, has spurts during growth, metabolic rate shows a similar pattern (Fig. 6(c)). When adulthood is reached, the spurts in metabolic rate also disappear. This suggests that if the second model truly reveals the underlying mechanisms responsible for long period cyclic growth, such as those we find in teeth and bone, one would not observe an oscillation in metabolic rate in the adult organism. The fine step-wise change in metabolic rate (or spurt) can only possibly be seen when animals are growing. Long term metabolite data collecting presently underway is expected to facilitate more fine-tuning of Model 2.

Model 1 and 2 are null hypotheses at two extremes. If we see an oscillation in BMR in adult animals, then Model 1 is probably right. If there is no BMR oscillation in adult animals, then Model 2 is likely more correct, and we should be able to see step-wise changes in metabolic rate in growing animals along with metabolite variation due to SMR resource allocations with high-resolution measurements.

8. SCN and HHO as proximate targets of selection

In their compendium of primate life history, Harvey and Clutton Brock ask, "does size exert a causal influence on life histories or could these differences be a consequence of some other variable that is closely related to size?" (p. 559) (Harvey and Clutton-Brock, 1985). We will argue here that size does exert a causal influence, and that the proximate objects of selection for body size and life history variability ultimately trace to variations in hypothalamic function.

The adaptation shared by all light-sensitive organisms is the to and fro of their biology in phase with daily astronomical rhythms (e.g., oscillations of metabolism, physiology, behavior). In mammals, the retino-hypothalamic pathway inputs light signals to the SCN, which centrally integrates these signals among a number of specialized hypothalamic nuclei. The SCN thus operates as a rheostatic multichannel device for efficaciously separating diverse hypothalamic processes and outputs to various times of the 24 h day. Circadian oscillators are thus an indubitable adaptation to the geophysical imperative of our world, and the SCN may be considered a proximal object of selection.

In Section 6.3 we advanced the idea that fast growth and high SMR are necessarily coupled with small body mass and low BMR because of energetic and ecological constraints. We suggest that overarching regulation of RI=1 primate biology and body size is coordinated by the SCN and its circadian output circuitry (many other RI=1 mammal groups are also similarly regulated). By this we mean that SCN-generated circadian rhythms establish limits on the extent to which characteristics manifested by other nuclei may be selected. The modularity of hypothalamic structure means that the SCN is not one thing, but rather an integrator of more than a few things, entraining many hypothalamic nuclei to the length of day and coordinating autonomic outputs to the whole body. Contributing to this is architectural complexity, including connections among the various nuclei.

Of course, there is variability in body size even among RI=1 primates and mammals. Thus proximate objects of selection must also include individual (e.g., arcuate nucleus) or multiple elements of the SCN-integrated set of hypothalamic nuclei responsible for controlling metabolism and rates of cell proliferation and that contribute to RI=1 primate body size variability (see Section 6.3). We can extend this concept and suggest that limited variability in life history characteristics among RI=1 primates also arise from selection on a respective specific nucleus or integrated set of regulating nuclei. The high levels of covariation between life history characteristics discussed in Section 6.2 implies, however, that the constraints of an overriding circadian biology mediate the SCN-integrated hypothalamic regulation of body mass during the formation of a life history matrix in RI=1-sized primates. Nevertheless, the question remains moot regarding whether the proximate objects of selection are those SCN-integrated nuclei that regulate body size specifically (and that, in turn, largely generate life history variability) or to those nuclei that regulate specific aspects of life history (and that, in turn, largely generate body size variability), or some combination thereof. The results reported in Section 5 suggest that the former predominates; the analytical means of evaluating the hypothalamic targets of selection on a taxon by taxon basis must be possible.

The HHO represents a centrally regulated and oscillating adjustable long-period rhythm responsible for RI $\geq$ 2 primate body size variability, which we suggest uses the set of SCN-integrated hypothalamic nuclei to manifest its effects on life history variability (see Section 6.4). Just as the SCN is a proximate object of selection, so must be the HHO. We have no information on the hypothalamic origin of the HHO, but we conjecture that it transmits signals (excitatory and/or inhibitory signals yet to be determined) to regulate body mass and, through the set of SCN-integrated hypothalamic nuclei, to regulate life history as it does for RI=1 primates. This is the basis for covariation of life history characteristics described in Section 6.2. Similarly, as described for RI=1 primates above, there is naturally some body size and life history variability among taxa with the same RI. The cause of this variability is the same, arising from a potentially multifarious set of proximate objects of selection that are SCN-integrated in the hypothalamus. In this case, however, it is key that selection for specific body size and life history adaptations occur within the constraints of overriding long period biological timing of as yet unknown hypothalamic origin operating through daily biological clock machinery residing in the SCN.

For instance, in a manner similar to primates, elephant RI scales positively with body mass (Bromage et al., 2009). In this case, island dwarfing from an ancestral large elephant is considered to be a result of selection for decreased age at sexual maturity owing to density dependent extrinsic mortality affecting small founding populations of large elephants on islands (Bromage et al., 2002). A dramatic reduction in body mass is observed to evolve, accompanied by an RI of 6, which is less than half the value of its putative ancestor. Selection for decreased age at sexual maturity is hypothesized to operate on variability in body size and, thus ultimately the HHO, to result in decreased size and an abbreviated life history.

However, that the primate production function is reduced compared to other mammals of the same body size (Charnov and Berrigan, 1993), is further evidence of a link between the HHO and rates of cell proliferation, but it also suggests that other objects of selection are involved. For both primates and elephants alike, RI scales positively with body mass. However, elephants have the capacity to grow to much larger body sizes for their RI than primates. Thus some proximate selection on the response elements of cells to signals to divide is at work among primates, diminishing the number of dividing cells with each cycle of the HHO. This is most likely a function of the rheostatic multichannel device described above.

Finally, this has been a very simplified explanation of the ultimate sources of selection. The actual causal pathway must be rich with taxon-specific complexity, but certain generalities can be made concerning mammals generally and primates specifically. Variability in density dependent extrinsic mortality selects for age at sexual maturity (Charnov, 1991), but not directly. Age at sexual maturity, like other life history, mass, and metabolic characteristics is determined by endocrine responses to pituitary functions regulated by hypothalamic outputs responsible for the growth, development, and maintenance of HHO regulated body mass. Thus the SCN-integrated hypothalamic nuclei and the HHO are ultimate targets of selection, selecting for age at sexual maturity by way of selecting its covariation with body mass. Of course, variability may be targeted by selection at any level, including the pituitary and its endocrine targets, which may fine tune life history responses to selection. The overarching regulation of body mass, however, arises from ultimate selection on the HHO.

While hypothalamic regulation of the pituitary and the resultant endocrine functions are key, leptin-mediated regulation of hypothalamic function by the brainstem's raphe nuclei are also fundamental to the skeleton's regulation of whole-body (bone) mass, metabolism, and reproduction (Karsenty and Ferron, 2012). Thus elements of the leptin signaling cascade and brainstem nuclei are also substantive objects of selection. Furthermore, the raphe nuclei project to the SCN (Hay-Schmidt et al., 2003), increasing the hypothalamic capacity to integrate all daily and HHO long period biological rhythms for establishing organismal life history. At the end of Section 2 we explained that evidence for the long period clock emerged from an unlikely place, the skeleton, but this is not surprising now that we recognize the skeleton to be fundamental to vertebrate life history, as demonstrated by this recent brain research.

9. Conclusions

Slow growing and larger bodied mammals (i.e., those with RI $\geq$ 2) have protracted life histories that would predict long-period physiological and developmental regulation. A long-period rhythm explains how the slow growth rate and protracted life history of a large-bodied primate can be achieved, say, by cells of many tissues proliferating on a longer period than that of a circadian rhythm. The resultant decrease in SMR due to reduced rates of cell proliferation means also that this long-period rhythm must be responsible for rates of metabolism-mediated maintenance over the lifetime. That the exact RI is preserved in both the ontogenetic development of bone and in the deposition of bone in adult life (e.g., in bone remodeling) (Bromage et al., 2009) is one indication that RI is a response to fundamental, albeit variable, biological timing.

A long-period physiological rhythm has been demonstrated in the adult human, recognized as a circaseptan (near 7-day) periodicity in heart rate and pressure (Appenzeller et al., 2005; Rawson et al., 2000; Wu et al., 1990). It has been specifically suggested that this centrally regulated autonomic, sympathetic-mediated heart rate and pressure oscillation in humans relates to RI (Appenzeller et al., 2005), which has a modal frequency of 8 days (Schwartz et al., 2001; Smith, 2008). We conjecture that the resemblance between the near-weekly variability in sympathetic drive (tone) and striae of Retzius formation in humans is no coincidence, and that they are physiological manifestations of a centrally regulated biological rhythm, the HHO, driven by an oscillator, and incidentally causing RI in enamel. The relationship that this physiological coupling has with the link between estrous

cyclicity and blood pressure discussed in Section 6.4, remains to be investigated, but it may correspond with enigmatic longer period rhythms in humans that have been observed at length scales measured in several weeks (Bromage et al., 2011) (see also Koukkari and Sothern, 2006).

We have established the hypothesis that the HHO regulates primate life history by means of body mass-dependent, mass-independent, and metabolic rate variation, and that body mass, reproduction, and metabolism are centrally linked to the HHO, which acts as a mediating mechanism in the regulation of life history according to metabolic constraints (Brown and Sibly, 2006). The HHO is further hypothesized to regulate postnatal cell proliferation rates of many tissues. Cell division rates in vivo appear to regulate longevity (Magalhães and Faragher, 2008), and thus the integrative study of long period rhythms and local aging mechanisms (e.g., neuroendocrine imbalance, DNA repair and metabolism, and related genetic disorders) is also expected to provide insight on their combined influence on longevity and the aging process.

In conclusion, we provide evidence of long period rhythmicity controlling primate life history. Because the regulation of such rhythms must involve the circadian timekeeper, evolution of long-period HHO biological timing is most likely a result of positive selection on hypothalamic neurosecretory performance using elements of clock function to modulate rates of development and metabolism. Notably, "As we experimentally dismantle the clock, the interdependence of timing and energetics seems inextricable" (Bass and Takahashi, 2010) (p. 1354). We extend the interdependence of timing and energetics to evolution of the HHO, representing a centrally regulated and oscillating adjustable long-period rhythm responsible for many aspects of organismal behavior, metabolism, and life history.

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Appendix A. Supplementary Information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.jtbi.2012.04.007.

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Appendix A

Table A1
Primate striae of Retzius repeat intervals in relation to body mass (kg).

Genus	Species	Sex	Striae of Retzius Repeat Interval[a]	Body Mass (kg)[a]
Catarrhines				
Afropithecus§	*turkanensis*	?	8	34.5
Dryopithecus§	*laietanus*	?	7	23
Erythrocebus	*patas*	F	4	4.8
Gigantopithecus§	*blacki*	?	11	300
Gorilla	*gorilla*	F	9	75.7
Gorilla	*gorilla*	M	10	169.3
Graecopithecus§	*freybergi*	M	8	63
Homo	*sapiens*	F	8	53.6
Homo	*sapiens*	M	8	60.2
Hylobates	*lar*	?	4	5.6
Hylobates	*syndactylus*	F	4.5	10.7
Macaca	*nemestrina*	F	4	7.8
Pan	*troglodytes*	F	6	31.1
Pan	*troglodytes*	M	6	40.5
Papio	*anubis*	M	7	21
Papio	*hamadryas*	F	7	9.4
Pongo	*pygmaeus*	F	10	35.8
Pongo	*pygmaeus*	M	10	78.3
Proconsul§	*heseloni*	?	5	10.5
Proconsul§	*nyanzae*	?	6	35
Semnopithecus	*entellus priam*	F	5	9.9
Theropithecus	*gelada*	F	7	13.6
Theropithecus	*gelada*	M	7	20.5
Platyrrhines				
Alouatta	*sp.*	M	6	5.99
Aotus	*sp.*	F	3	0.772
Callimico	*goeldii*	F	3	0.463
Callithrix	*humeralifer*	F	3	0.35
Callithrix	*jacchus*	?	1	0.32
Callithrix	*pygmaea*	F	1	0.122
Cebus	*albifrons*	M	6	3.18
Cebus	*albifrons*	F	5	2.29
Cebus	*apella*	M	5	3.65
Cebus	*apella*	F	4	2.52

Cebus	*capucinus*	F	4	2.54
Cebus	*capucinus*	M	6	3.68
Cebus	*capucinus*	M	6	3.68
Cebus	*olivaceus*	M	4	3.29
Leontopithecus	*rosalia*	?	3	0.6
Saguinus	*fuscicollis*	?	2	0.343
Saguinus	*nigricollis*	F	2	0.45
Saguinus	*oedipus*	F	1	0.404
Saimiri	*boliviensis*	F	3	0.711
Saimiri	*oerstedii*	M	3	0.897
Saimiri	*sciureus*	M	3	0.779
Strepsirhines				
Nycticebus	*sp.*	?	2	0.679

Striae of Retzius values obtained primates of known sex ("F" for female and "M" for male) were compared to body mass. The body mass species mean was used in statistical comparisons when the sex was not known.

a. Data obtained from Bromage et al (Bromage et al. 2009).

Table A2
Primate striae of Retzius repeat intervals (RI) in relation to life history characteristics[a].

Genus Species	RI [b]	Gestation Length (d)	Birth Weight (gm)	Lactation Length (d)	Estrous Cycle Length (d)	Age at First Breeding (mo)	Age at Sexual Maturity	Lifespan (yr)	Interbirth Interval (d)	Neonatal Brain Weight
Catarrhines										
Erythrocebus patas	4	163		222[e]		36	33	20.2	420	
Gorilla gorilla	9.5	256	2110	1583	28	118.2	78	39.3	1460	227
Homo sapiens	8.9	267	3300	720	28	232	198	70	1440	384
Hylobates lar	4	205	410.5	730	27	90[g]	61[g]	31.5	969	50.1
Hylobates syndactylus	4.5	231	517							
Macaca nemestrina	4	167	473	365		47.3	35	26.3	405	66
Pan troglodytes	6	228	1756	1460	36	138	118	44.5	1825	128
Papio anubis	7	180	1068	420	31				420	
Papio hamadryas	7	172		450[f]				35.6		
Pongo pygmaeus	10	260	1728	1095	30	128	84	50	1025	170.3
Theropithecus gelada	7	170	464	450		54	49.5		525	
Platyrrhines										
Alouatta palliata	6	187	480	630	16	45	45		675	30.8
Aotus trivirgatus	3	133	98	76[c]					220	
Callimico goeldii	3	154	48.6	65	27	15.8	8.5		167	5.8
Callithrix jacchus	1	148	28	63	16	17	12	12	157	4.4
Callithrix pygmaea	1	136	16	90		24		10	154	
Cebus albifrons	5.5		234	270			43.1			
Cebus apella	4.5	160	248		18	42		40		
Cebus capucinus	5		230							29
Leontopithecus rosalia	3	129	53.6	90		35.6		14	304	
Saguinus fuscicollis	2		40	90		24.1			242	
Saguinus nigricollis	2		43.5	80						
Saguinus oedipus	1	145	43.2	66[d]	16		18	13	280	4.9
Saimiri sciureus	3	170	195	243[c]	18	46.3		21	414	
Strepsirhines										
Nycticebus coucang	2	193	49.3	90	40			14.5		4

a. Data obtained from Harvey and Clutton-Brock (Harvey and Clutton-Brock 1985) except where noted.
b. Data obtained from Bromage et al (Bromage et al. 2009); sexes within species were averaged.
c. Data obtained from Isler et al. (Isler et al. 2008).
d. Data obtained from Lindenfors (Lindenfors 2002).
e. Data obtained from Barrickman et al. (Barrickman et al. 2008).
f. Data obtained from Walker (Nowak 1991).
g. Data obtained from Geissmann (Geissmann 1991),
h. Data obtained from Wildpro (Wildpro 2011).

Table A3
Primate striae of Retzius repeat intervals in relation to adult endocranial volume (ECV).

Genus	Species	Striae of Retzius Repeat Interval[a]	ECV male mean[b]	ECV female mean[b]	ECV species mean[b]
Catarrhines					
Erythrocebus	*patas*	4 F		88.86	
Gorilla	*gorilla*	10 M, 9 F			490.41
Hylobates	*lar*	4.00		101.87	
Hylobates	*syndactylus*	4.5 F		122.45	
Macaca	*nemestrina*	4 F		100.65	
Pan	*troglodytes*	6 M, 6 F			368.35
Papio	*anubis*	7 M	182.40		
Papio	*hamadryas*	7 F		133.00	
Pongo	*pygmaeus*	10 M, 10 F			377.38
Theropithecus	*gelada*	7 M, 7 F			133.33
Semnopithecus	*priam*	5 F		78.28	
Platyrrhines					
Aotus	*azarae*	3 F		20.69	
Aotus	*lemurinus*	3 F		16.25	
Aotus	*trivirgatus*	3 F		16.13	
Alouatta	*belzebul*	6 M	54.50		
Alouatta	*caraya*	6 M	57.46		
Alouatta	*guariba*	6 M	54.32		
Alouatta	*palliata*	6 M	51.71		
Alouatta	*pigra*	6 M	53.50		
Alouatta	*seniculus*	6 M	56.19		
Callimico	*goeldii*	3 F		11.90	
Callithrix	*humeralifer*	3 F		8.20	
Callithrix	*jacchus*	1.00			7.24
Callithrix	*pygmaea*	1 F		4.33	
Cebus	*albifrons*	6 M, 5 F			65.46
Cebus	*apella*	5 M, 4 F			66.63
Cebus	*capucinus*	6 M, 4 F			72.93
Cebus	*olivaceus*	4 M	71.29		
Leontopithecus	*rosalia*	3.00			12.84
Saguinus	*fuscicollis*	2.00			7.94
Saguinus	*nigricollis*	2 F			
Saguinus	*oedipus*	1 F		9.92	
Saimiri	*boliviensis*	3 M	25.64		
Saimiri	*oerstedii*	3 M	24.61		

Saimiri	*sciureus*	3 M	24.26		
Platyrrhines					
Nycticebus	*bengalensis*	2.00			10.28
Nycticebus	*coucang*	2.00			10.28
Nycticebus	*pygmaeus*	2.00			10.28

Striae of Retzius values obtained primates of known sex ("F" for female and "M" for male) were compared to ECV means for their respective sex. When Striae of Retzius values for both sexes of a single species were available, the mean value was compared to the ECV species mean in statistical comparisons. The ECV species mean was also used in statistical comparisons when the sex was not known.

a. Data obtained from Bromage et al (Bromage et al. 2009).

b. Data obtained from Isler et al. (Isler et al. 2008).

Table A4
Hominin striae of Retzius repeat intervals in relation to endocranial volume (ECV).

A			
Genus	Species	Striae of Retzius Repeat Interval[a]	ECV species mean[b]
Pan	*troglodytes*	6.0	368
Australopithecus	*afarensis*	7.0	430
Australopithecus	*africanus*	7.2	457
Paranthropus	*roubusts*	6.9	542
Paranthropus	*boisei*	7.0	491
Homo	*rudolfensis*	7.7	757
Homo	*erectus/ergaster*	8.0	869
Homo	*sapiens*	8.9	1350

B

Genus	Species	Specimen	ECV	ECV Reference
Pan	*troglodytes*		368.35	(Isler et al. 2008)
Australopithecus	*afarensis*	AL 333-45	500.00	(Holloway 1983)
Australopithecus	*afarensis*	AL 333-105	343.00	(Falk 1987)
Australopithecus	*afarensis*	AL 162-28	375.00	(Falk 1987)
Australopithecus	*afarensis*	AL 444-2	500.00	(Johanson and Edgar 1996)
Australopithecus	*africanus*	MLD 37/38	425.00	(Holloway 1975)
Australopithecus	*africanus*	MLD 3	387.5 (375-400)	(Wolpoff 1997)
Australopithecus	*africanus*	MLD 1	500.00	(Holloway 1975)
Australopithecus	*africanus*	Sts 60	428.00	(Holloway 1975)
Australopithecus	*africanus*	Sts 71	428.00	(Holloway 1975)
Australopithecus	*africanus*	Sts 5	485.00	(Holloway 1975)
Australopithecus	*africanus*	Sts 19	436.00	(Holloway 1975)
Australopithecus	*africanus*	Stw 505	586.00	(Hawks and Wolpoff 1999)
Australopithecus	*africanus*	Taung Child	440.00	(Holloway 1975)
Paranthropus	*roubusts*	Kromdraai B	650	(Tobias 1971)
Paranthropus	*roubusts*	SK 1585	476	(Falk et al. 2000)
Paranthropus	*roubusts*	SK 54	500	(Beals et al. 1984)
Paranthropus	*boisei*	Omo L338y-6	427	(Holloway 1981)
Paranthropus	*boisei*	KNM-ER 23000	491.00	(Brown et al. 1993)
Paranthropus	*boisei*	KNM-ER	475 (450-500)	(Brown et al. 1993)

		13750		
		KNM-ER		
Paranthropus	*boisei*	17400	395 (390-400)	(Holloway 1988)
Paranthropus	*boisei*	OH 5	500.00	(Falk et al. 2000)
Paranthropus	*boisei*	Omo 323	490.00	Brown et al 1993
Paranthropus	*boisei*	KNM-ER 406	525.00	(Holloway 1988)
Paranthropus	*boisei*	KNM-ER 407	438.00	(Falk et al. 2000)
Paranthropus	*boisei*	KNM-ER 732	466.00	(Falk et al. 2000)
		KNM-ER		
Paranthropus	*boisei*	13750	480.00	(Holloway 1988)
		KNM-ER		
Paranthropus	*boisei*	23000	491.00	(Brown et al. 1993)
Paranthropus	*boisei*	Chesowanja 1	550.00	(Carney et al. 1971)
Paranthropus	*boisei*	Konso	545.00	(Suwa et al. 1997)
		KNM-ER		
Homo	*rudolfensis*	1470	700.00	(Bromage et al. 2008)
		KNM-ER		
Homo	*rudolfensis*	3732	700.00	(Stringer 1986)
		KNM-ER		
Homo	*rudolfensis*	1590	870.00	Beals 1984
Homo	*erectus*	OH 9	1067.00	(Holloway 1983)
Homo	*erectus*	OH 12	727.00	(Holloway 1983)
		KNM-ER		
Homo	*ergaster*	3733	848.00	(Holloway 1983)
		KNM-ER		
Homo	*ergaster*	3883	804.00	(Holloway 1983)
		KNM-WT		
Homo	*ergaster*	15000	900.00	(Holloway 1983)
Homo	*sapiens*		1350.00	Reid (unpublished)

a. Data obtained from Bromage et al (Bromage et al. 2009).
b. Data obtained from means calculated from specimens listed in Table 3B.

Table A5
Primate striae of Retzius repeat intervals in relation to basal metabolic rate (W).

Genus	Species	Striae of Retzius Repeat Interval[a]	Species avg. BMR (W)
Callithrix	*jacchus*	1	848[b]
Callithrix	*pygmaea*	1	599[b]
Alouatta	*palliata*	6	11464[b]
Aotus	*trivirgatus*	3	2499[b]
Saimiri	*sciureus*	3	4429[b]
Erythrocebus	*patas*	4	5958[b]
Papio	*hamadryas*	7	21095[b]
Homo	*sapiens*	8	82780[b]
Callimico	*goeldii*	3	1552[c]
Saguinus	*oedipus*	1	2789[c]
Pan	*troglodytes*	6	50247[c]
Pongo	*pygmaeus*	10	27586[c]
Leontopithecus	*rosalia*	3	2130[c]

a. Data obtained from Bromage et al (Bromage et al. 2009).
b. Data obtained from Savage et al. (Savage et al. 2004).
c. Data in obtained from Isler et al. (Isler et al. 2008) and converted from ml O_2/hr to W.

Table A6
Primate striae of Retzius repeat intervals, specific metabolic rate (Kcal per gm of body mass per day), and bone cell density.

Genus	Species	Striae of Retzius Repeat Interval[a]	SMR (Kcal/gm body mass per day)[b]	Osteocyte Density[a]
Homo	*sapiens*	9	23.6	20444
Pan	*troglodytes*	6	27.9	18706
Gorilla	*gorilla*	9	19.7	
Pongo	*pygmaeus*	10	35.1	
Papio	*anubis*	7	43.2	
Macaca	*mulatta*	4	37	22222
Cercopithecus	*aethiops*		43.4	32012
Galago	*crassicaudatus*		68.4	44353

a. Data obtained from Bromage et al (Bromage et al. 2009).
b. Data obtained from Tolmasoff et al. (Tolmasoff et al. 1980).

Table A7

Correlation matrix of primate striae of Retzius repeat intervals (RI) against life history traits and metabolic rate (all primates for which RI is available were used). Significant correlations are bold.

		Variable													
Variable		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
1 RI															
2 BODY MASS	*r*	**.899**													
	p	.000													
	N	29													
3 ESTROUS LENGTH	*r*	.453	.485												
	p	.120	.093												
	N	13	13												
4 BIRTH WEIGHT	*r*	**.916**	**.978**	.416											
	p	.000	.000	.158											
	N	23	22	13											
5 GESTATION LENGTH	*r*	**.692**	**.811**	**.610**	**.838**										
	p	.001	.000	.027	.000										
	N	21	20	13	19										
6 LACTATION LENGTH	*r*	**.855**	**.929**	.368	**.941**	**.843**									
	p	.000	.000	.239	.000	.000									
	N	22	21	12	20	19									
7 INTERBIRTH INTERVAL	*r*	**.804**	**.884**	.590	**.916**	**.908**	**.946**								
	p	.000	.000	.056	.000	.000	.000								
	N	18	17	11	17	17	18								
8 AGE AT SEXUAL MATURITY	*r*	**.787**	**.902**	.590	**.948**	**.887**	**.899**	**.958**							
	p	.001	.000	.094	.000	.000	.000	.000							
	N	13	13	9	12	12	13	12							
9 AGE AT FIRST BREEDING	*r*	**.809**	**.885**	**.638**	**.931**	**.900**	**.905**	**.956**	**.980**						
	p	.000	.000	.047	.000	.000	.000	.000	.000						
	N	16	16	10	15	15	15	15	11						
10 LIFESPAN	*r*	**.918**	**.919**	.434	**.960**	**.820**	**.921**	**.942**	**.981**	**.911**					
	p	.000	.000	.210	.000	.000	.000	.000	.000	.000					
	N	15	15	10	13	15	14	12	9	12					
11 NEONATAL BRAIN WEIGHT	*r*	**.897**	**.977**	.360	**.988**	**.865**	**.928**	**.914**	**.942**	**.965**	**.972**				
	p	.000	.000	.308	.000	.001	.000	.000	.000	.000	.000				
	N	12	12	10	12	11	11	10	10	9	9				
12 ADULT ENDOCRANIAL VOLUME	*r*	**.875**	**.972**	.452	**.984**	**.824**	**.918**	**.908**	**.948**	**.925**	**.956**	**.993**			
	p	.000	.000	.121	.000	.000	.000	.000	.000	.000	.000	.000			
	N	39	29	13	23	21	22	18	13	16	15	12			
13 BMR (W)	*r*	**.876**	**.968**	.655	**.986**	**.889**	**.916**	**.980**	**.982**	**.945**	**.978**	**.971**	**.972**		
	p	.000	.000	.078	.000	.000	.000	.000	.000	.000	.000	.000	.000		
	N	13	12	8	11	13	13	12	8	10	10	7	13		
14 SMR (KCAL)	*r*	-.456	-.798	.370	-.789	-.716	-.664	-.806	-.120	-.132	.142	-.514	-.728	**-.999**	
	p	.364	.105	.540	.113	.174	.221	.100	.880	.868	.858	.486	.163	.024	
	N	6	5	5	5	5	5	5	4	4	4	4	5	3	

Table A8

Correlation matrix of primate striae of Retzius repeat intervals (RI) against life history traits and metabolic rate (all primates except those with RI=1 were used). Significant correlations are bold.

		Variable													
Variable		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
1 RI (w/o RI=1)															
2 BODY MASS	*r*	**.927**													
	p	.000													
	N	26													
3 ESTROUS LENGTH	*r*	.014	.485												
	p	.968	.093												
	N	11	13												
4 BIRTH WEIGHT	*r*	**.919**	**.978**	.416											
	p	.000	.000	.158											
	N	20	22	13											
5 GESTATION LENGTH	*r*	**.646**	**.811**	**.610**	**.838**										
	p	.004	.000	.027	.000										
	N	18	20	13	19										
6 LACTATION LENGTH	*r*	**.860**	**.929**	.368	**.941**	**.843**									
	p	.000	.000	.239	.000	.000									
	N	19	21	12	20	19									
7 INTERBIRTH INTERVAL	*r*	**.776**	**.884**	.590	**.916**	**.908**	**.946**								
	p	.001	.000	.056	.000	.000	.000								
	N	15	17	11	17	17	18								
8 AGE AT SEXUAL MATURITY	*r*	**.771**	**.902**	.590	**.948**	**.887**	**.899**	**.958**							
	p	.006	.000	.094	.000	.000	.000	.000							
	N	11	13	9	12	12	13	12							
9 AGE AT FIRST BREEDING	*r*	**.800**	**.885**	**.638**	**.931**	**.900**	**.905**	**.956**	**.980**						
	p	.001	.000	.047	.000	.000	.000	.000	.000						
	N	14	16	10	15	15	15	15	11						
10 LIFESPAN	*r*	**.877**	**.919**	.434	**.960**	**.820**	**.921**	**.942**	**.981**	**.911**					
	p	.000	.000	.210	.000	.000	.000	.000	.000	.000					
	N	12	15	10	13	15	14	12	9	12					
11 NEONATAL BRAIN WEIGHT	*r*	**.902**	**.977**	.360	**.988**	**.865**	**.928**	**.914**	**.942**	**.965**	**.972**				
	p	.000	.000	.308	.000	.001	.000	.000	.000	.000	.000				
	N	10	12	10	12	11	11	10	10	9	9				
12 ADULT ENDOCRANIAL VOLUME	*r*	**.887**	**.972**	.452	**.984**	**.824**	**.918**	**.908**	**.948**	**.925**	**.956**	**.993**			
	p	.000	.000	.121	.000	.000	.000	.000	.000	.000	.000	.000			
	N	36	29	13	23	21	22	18	13	16	15	12			
13 BMR (W)	*r*	**.909**	**.968**	.655	**.986**	**.889**	**.916**	**.980**	**.982**	**.945**	**.978**	**.971**	**.972**		
	p	.000	.000	.078	.000	.000	.000	.000	.000	.000	.000	.000	.000		
	N	10	12	8	11	13	13	12	8	10	10	7	13		
14 SMR (KCAL) [a]	*r*	**-.977**	-.798	.370	-789	-716	-664	-806	-120	-132	.142	-.514	-.728	**-.999**	
	p	.023	.105	.540	.113	.174	.221	.100	.880	.868	.858	.486	.163	.024	
	N	4	5	5	5	5	5	5	4	4	4	4	5	3	

a. Test was made without the hypometabolic *Pongo* and *P. anubis* for RI vs SMR only.

Table A9

Partial correlation matrix of primate striae of Retzius repeat intervals (RI) against life history traits and metabolic rate whilst controlling for body mass (all primates for which RI is available were used). Significant correlations are bold.

			Variable												
Control	Variable		**1**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
2	**1**	*r*													
BODY	RI	*p*													
MASS		df													
	3	*r*	.045												
	ESTROUS	*p*	.889												
	LENGTH	df	10												
	4	*r*	.394	-.322											
	BIRTH	*p*	.077	.307											
	WEIGHT	df	19	10											
	5	*r*	-.148	.424	.366										
	GESTATION	*p*	.545	.169	.136										
	LENGTH	df	17	10	16										
	6	*r*	.118	-.255	.410	.412									
	LACTATION	*p*	.619	.449	.082	.090									
	LENGTH	df	18	9	17	16									
	7	*r*	.046	.394	**.533**	**.698**	**.723**								
	INTERBIRTH	*p*	.865	.261	.033	.003	.002								
	INTERVAL	df	14	8	14	14	14								
	8	*r*	-.131	.406	**.737**	**.614**	.380	**.797**							
	AGE AT	*p*	.685	.319	.010	.044	.223	.003							
	SEXUAL	df	10	6	9	9	10	9							
	MATURITY														
	9	*r*	.066	.514	**.673**	**.667**	.482	**.798**	**.906**						
	AGE AT FIRST	*p*	.816	.157	.008	.009	.081	.001	.000						
	BREEDING	df	13	7	12	12	12	12	8						
	10	*r*	**.534**	-.032	**.753**	.323	.463	**.702**	**.893**	.531					
	LIFESPAN	*p*	.049	.935	.005	.261	.111	.016	.003	.093					
		df	12	7	10	12	11	9	6	9					
	11	*r*	.196	-.619	**.730**	.584	.245	.512	.659	**1.000**	**.893**				
	NEONATAL	*p*	.564	.076	.011	.077	.496	.159	.054	.000	.003				
	BRAIN	df	9	7	9	8	8	7	7	6	6				
	WEIGHT														
	12	*r*	.012	-.096	**.689**	.260	.167	.446	**.706**	**.596**	**.682**	**.859**			
	ADULT	*p*	.953	.767	.001	.283	.481	.083	.010	.019	.007	.001			
	ENDOCRANIAL	df	26	10	19	17	18	14	10	13	12	9			
	VOLUME														
	13	*r*	.042	**.849**	**.742**	**.706**	.177	**1.000**	**1.000**	**.754**	**.896**	.472	.528		
	BMR (W)	*p*	.901	.016	.014	.015	.602	.000	.000	.019	.001	.344	.095		
		df	9	5	8	9	9	9	5	7	7	4	9		
	14	*r*	**.997**	**1.000**	-.064	-.193	.349	-.356	**1.000**	**1.000**	**1.000**	**1.000**	.335	.	
	SMR (KCAL)	*p*	.003	.000	.936	.807	.651	.644	.000	.000	.000	.000	.665	.	
		df	2	2	2	2	2	2	1	1	1	1	2	0	

Table A10
Residuals arising from the regression of primate striae of Retzius repeat intervals against body size (RIr) are regressed against life history traits and metabolic rate. Significant relationship is in bold. In all tests of association between RIr and primate life history traits, regressions were performed with (w/) and without (w/o) RI=1 taxa if present in the data set. In the test of association between RIr and BMR, an additional test was made without RI=1 taxa and the hypometabolic *Pongo*. In the test of association between RI and SMR, an additional test was made without the hypometabolic *Pongo*. See Discussion.

Tests of Association	Regression Variation	*R* value	*P* value	R^2 value (adjusted)	Slope
RIr vs Body mass (kg)	w/RI=1	0.000	= 1.000	-0.037	0.000
	w/o RI=1	0.000	= 1.000	-0.042	0.000
RIr vs Gestation length (days)	w/RI=1	0.038	= 0.872	-0.054	0.051
	w/o RI=1	0.195	= 0.454	-0.026	-0.163
RIr vs Birth weight (gm)	w/RI=1	0.169	= 0.452	-0.020	0.032
	w/o RI=1	0.128	= 0.602	-0.042	0.017
RIr vs Lactation length (days)	w/RI=1	0.170	= 0.461	-0.022	0.046
	w/o RI=1	0.47	= 0.562	-0.040	0.027
RIr vs Estrous cycle length (days)	w/RI=1	0.112	= 0.714	-0.077	0.111
	w/o RI=1	**0.669**	= 0.024	0.387	0.404
RIr vs Age at first breeding (months)	w/RI=1	0.026	= 0.923	-0.071	-0.009
	w/o RI=1	0.115	= 0.696	-0.069	-0.025
RIr vs Age at sexual maturity (months)	w/RI=1	0.150	= 0.626	-0.066	0.058
	w/o RI=1	0.188	= 0.579	-0.072	-0.046
RIr vs Lifespan (years)	w/RI=1	0.435	= 0.105	0,127	0.210
	w/o RI=1	0.359	= 0.251	0.042	0.124
RIr vs Interbith interval (days)	w/RI=1	0.118	= 0.653	-0.052	0.044
	w/o RI=1	0.138	= 0.639	-0.063	-0.030
RIr vs Neonatal brain weight (gm)	w/RI=1	0.253	= 0.428	-0.030	0.051
	w/o RI=1	0.103	= 0.776	-0.113	0.014
RIr vs Adult endocranial volume (cc)	w/RI=1	0.044	= 0.821	-0.035	0.008
	w/o RI=1	0.042	= 0.840	-0.040	0.005
RIr vs Hominin endocranial volume (cc)		0.456	= 0.256	0.076	0.077
RIr vs BMR (Watts)	all taxa	0.257	= 0.420	-0.027	0.057
	w/o RI=1 & Pongo	0.320	= 0.440	-0.047	-0.033

RIr vs SMR (Kcal vs gm)	all taxa	0.452	= 0.445	-0.061	0.210
	w/o Pongo	0.302	= 0.698	-0.064	0.106

Table A11
Stepwise multiple regression of primate striae of Retzius repeat intervals (RI) against body mass and body mass including estrous length (no other life history trait or metabolic rate variable was a significant predictor in the model). Note that estrous length was excluded in models that included RI=1 primates. Missing values were handled by excluding cases "listwise" (this is a reason for a difference in the RI vs Body Mass *r*-value from Table 1).

Dependent Variable RI=2+
Adjusted R square = 0.929; F = 59.5, $p < 0.001$ (using the stepwise method).

Predictor Variable	*r*	*Beta*	*p*
Body Mass	0.944	0.267	< 0.001
Estrous Length	0.972	0.466	= 0.037

Table A12

Partial correlation matrix of primate striae of Retzius repeat intervals (RI) against life history traits and metabolic rate whilst controlling for body mass and BMR (W) (all primates except those with RI=1 were used). Significant correlations are bold.

			Variable											
Control	Variable		**1**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**14**
2	**1**	*r*												
BODY	RI	*p*												
MASS		df												
13	**3**	*r*	**-1.000**											
BMR	ESTROUS	*p*	.000											
(W)	LENGTH	df	4											
	4	*r*	.098	**-1.000**										
	BIRTH	*p*	.817	.000										
	WEIGHT	df	6	4										
	5	*r*	-.028	-.780	.421									
	GESTATION	*p*	.947	.068	.259									
	LENGTH	df	6	4	7									
	6	*r*	**-.806**	-.467	-.333	.411								
	LACTATION	*p*	.016	.351	.381	.238								
	LENGTH	df	6	4	7	8								
	7	*r*	.	.	.	.	.							
	INTERBIRTH	*p*	.	.	.	.	.							
	INTERVAL	df	6	4	7	8	8							
	8	*r*	.	.	.	.	.	.						
	AGE AT	*p*	.	.	.	.	.	.						
	SEXUAL	df	4	4	4	4	4	4						
	MATURITY													
	9	*r*	-.320	-.364	.257	.539	.290	.	.					
	AGE AT FIRST	*p*	.440	.478	.539	.168	.487	.	.					
	BREEDING	df	6	4	6	6	6	6	4					
	10	*r*	.154	**-1.000**	.296	.696	**-.987**	.	.	-.499				
	LIFESPAN	*p*	.716	.000	.477	.055	.000	.	.	.208				
		df	6	4	6	6	6	6	4	6				
	11	*r*	-.114	**-1.000**	.642	.185	.401	.	.	**1.000**	**1.000**			
	NEONATAL	*p*	.855	.000	.243	.765	.504	.	.	.000	.000			
	BRAIN	df	3	3	3	3	3	3	3	3	3			
	WEIGHT													
	12	*r*	-.256	**-1.000**	.522	.088	-.188	.	.	.355	.553	.814		
	ADULT	*p*	.541	.000	.149	.809	.603	.	.	.389	.155	.094		
	ENDOCRANIAL	df	6	4	7	8	8	8	4	6	6	3		
	VOLUME													
	14	*r*	.	.	.	.	.	.	.	.	.	.	.	
	SMR (KCAL)	*p*	.	.	.	.	.	.	.	.	.	.	.	
		df	0	0	0	0	0	0	0	0	0	0	0	

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