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Age-related changes in Thyroid hormone levels of bonobos and chimpanzees indicate heterochrony in development

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ABSTRACT

We present information on age related changes of thyroid hormone levels in bonobos ($N = 96$) and chimpanzees ($N = 100$) ranging between one and 56 years of age. Fresh urine samples were used for hormone measurements with a commercial competitive total triiodothyronine (T3) ELISA. In both species, immature individuals had higher TT3 levels than adults and there was a marked decrease in TT3 levels between age classes. The two species differed in terms of the timing of TT3 level changes, with chimpanzees experiencing a significant decline in TT3 levels after 10 years of age and bonobos after 20 years of age. The decline of TT3 in chimpanzees appears to coincide with the time when somatic growth terminates while TT3 values in bonobos decrease much later. This temporal asymmetry in urinary thyroid hormone levels indicates heterochrony in the ontogenetic changes of the two sister species and developmental delay in bonobos. The prolongation of high TT3 levels in bonobos, which is characteristic of immatures of both *Pan* species may affect the behavior of bonobos; namely, the low intensity of aggression they display. Given that developmental studies are often based on post-mortem analyses of skeletons, measures of urinary thyroid hormones offer a non-invasive tool for exploring ontogenetic changes in living wild and captive hominoids.

Introduction

Compared with other mammals, humans and hominoid primates share a suite of history traits such as slow maturation, delay in reproductive activity, and long life expectancy (Robson and Wood, 2008). Since information from prehistoric humans and early hominids is scarce, data from extant hominoid primates remains an important avenue for exploring human evolution. For this purpose studies on the two *Pan* species, bonobo (*Pan paniscus*) and chimpanzee (*Pan troglodytes*), have received particular attention and have been used, in conjunction with human data, to construct evolutionary models (Ponce de León and Zollikofer, 2008). Although both *Pan* species share certain patterns of ontogenetic development (Leigh and Shea, 1996; De Lathouwers and Van Elsacker, 2006), there are multiple lines of evidence showing that bonobos develop more slowly and that juvenile features in the dentition and cranial anatomy persist for a longer period of time (Shea, 1983; Lieberman et al., 2007; Durrleman et al., 2012). Data from studies exploring the development of social behaviors and cognitive skills also support the theory that the evolution of the two *Pan* species is, at least partially, shaped by heterochrony (temporal differences in the patterns of development) (Wobber et al., 2010a). Differences in the timing of developmental stages may affect both ontogeny and phylogeny (Gould, 1977), and are widely considered as prime movers in the context of human evolution (e.g., Gould, 1977; Godfrey and Sutherland, 1996). Accordingly, studying developmental processes of the two *Pan* species may provide reference points for reconstructing evolutionary changes during human evolution (Lockwood et al., 2004). Indeed, comparative data from the two *Pan* species have turned out to be useful for modeling developmental trajectories of craniofacial development in Neanderthals and modern humans (Ponce de León and Zollikofer, 2008).

Previous work on developmental processes in *Pan* species has largely focused on parameters such as skeletal growth, the dentition, and behavior, while corresponding information on endocrine parameters for growth control are largely missing. Thyroid hormones serve a central function in developmental processes (Crockford, 2002) and affect various physiological functions including metabolism, reproduction, and behavioral responses to stress (Hadley, 1988). The thyroid gland is present in all vertebrates

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(Silva, 2006) and the prohormone thyroxine (T4) is the predominant product secreted by this gland (Visser, 1994; Köhrle, 1999; Power et al., 2001). The three major forms of circulating thyroid hormones are thyroxine (3,3′,5,5′-Tetraiodo-L-thyronine, T4), triiodothyronine (3,3′,5-Triiodo-L-thyronine, T3), and reverse triiodothyronine (3,3′,5′-Triiodo-L-thyronine, rT3) (Refetoff and Nicoloff, 1995). The secretion of T4 and T3 is stimulated by the hypothalamic thyrotropin-releasing hormone (TRH), which stimulates the pituitary gland to secrete thyroid-stimulating hormone (TSH/thyrotropin). Thyroid-stimulating hormone activates the thyroid gland to secrete T3 and T4. The circulation of these thyroid hormones exerts negative feedback control on both TRH and TSH (Dumont and Vassart, 1995; Fisher, 1996). In human and animal studies, T3 and T4 have been measured in serum and urine (e.g., Gaitane et al., 1975; Yoshida et al., 1980; Wasser et al., 2010). In non-human primates, thyroid hormones have been measured in Great Apes (Miller et al., 1983; Suedmeyer, 1997; Lair et al., 1999) as well as in Old World and New World monkeys (Kaack et al., 1979; Arbelle et al., 1994).

Without thyroid hormones, most vertebrates would be unable to grow and reach their normal adult form (Porterfield and Hendrich, 1993). For instance, these hormones are essential for normal puberty in humans (Dunger et al., 1990) and non-human primates (Mann and Plant, 2010). Accordingly, there is marked variation in thyroid function with age (Fisher, 1996). Human studies show that excretion of T3 and T4 by the thyroid gland, increases sharply directly after birth and then reaches a high plateau, which gradually decreases around the age of ten years (Oliner et al., 1957; Beckers et al., 1966; Ryness, 1972; Hesch et al., 1977). There is controversy regarding sex-differences in thyroid hormone secretion. While some studies have not detected sex difference (e.g., AvRuskin et al., 1973; Fisher et al., 1977; Nelson et al., 1993), others report that levels decrease at the end of puberty in girls but not boys. Such a difference can be associated with differences in timing of growth (e.g., Garcia-Bulnes et al., 1977; Parra et al., 1980; Dunger et al., 1990).

In hominoid primates, previous work has explored the thyroid status in clinical contexts, for example investigating hypothyroidism (Miller et al., 1983; Suedmeyer, 1997; Lair et al., 1999). Yet, little is known about age-related changes, leaving the significance of thyroid hormones as markers for developmental changes largely unexplored. In male orangutans, urinary TSH levels vary between young and adult individuals, with adult orangutans having lower TSH levels than juvenile and developing individuals (Maggioncalda et al., 2000). Thyroid binding transthyretin (TTR) levels, a thyroid hormone binding protein, in the blood of bonobos and chimpanzees are twice as high as in humans, and both *Pan* species have higher serum levels of thyroid hormones than do humans (Gagneux et al., 2001). These differences in thyroid hormone metabolism have been highlighted as "… the first known endocrine difference between these [*Homo* and *Pan*] species…," and it is assumed that this difference may indicate permanently elevated thyroid hormone levels in *Pan* species (Gagneux et al., 2001). Therefore, thyroid hormones have the potential to reveal differences in closely related species.

Here we present the first data on age-related changes of thyroid hormones from bonobos and chimpanzees. The aim of this study is to explore if age-related changes in thyroid hormone levels occur in these species and, if present, to what extent the temporal changes show species-specific variation. Previous studies examining dentition (Boughner and Dean, 2008), post-cranial and cranial skeletal growth (Lieberman et al., 2007), and behavior and cognition (Wobber et al., 2010b) have suggested that development in bonobos is delayed when compared with chimpanzees (Shea, 1983). In fact, differences in the emergence of adult patterns of morphological and behavioral traits are considered landmarks for the divergent evolution of the two *Pan* species (Wobber et al., 2010a; Hare et al., 2012). While these studies suggest developmental differentiation between the two species, the underlying physiological parameters of development, such as thyroid hormones, remain to be investigated.

In the cross-sectional study presented here, we measured total T3 (TT3) levels in urine samples from captive bonobos ($N = 96$) and chimpanzees ($N = 100$), ranging from one to 56 years of age. Studies exploring thyroid hormones during ontogeny have shown that these hormones are an excellent marker for monitoring development. Based on the findings of studies on humans and hominoids, we expect to find higher TT3 levels in immature apes compared with adults. In humans – although this is still debated – the timing of the decrease in thyroid levels may vary with sex, with levels decreasing earlier in girls than boys (Parra et al., 1980) and this change in thyroid levels may coincide with sex differences in somatic growth (Dunger et al., 1990). Similar sex differences in body growth have been reported for the two *Pan* species (Leigh and Shea, 1995), and therefore we predict that males and females may also differ in the timing of the age related decrease in thyroid hormones. Considering the evidence suggesting developmental delay in bonobos, we expect that the decrease in thyroid hormones that characterizes the transition from adolescence to adulthood happens later in bonobos as compared with chimpanzees.

Material and methods

We measured urinary total T3 (TT3) levels in 96 urine samples obtained from 44 male and 52 female captive bonobos and 100 urine samples from 35 males and 65 female chimpanzees ranging from one to 56 years of age (Table A.1), which were assigned to six age categories (Table 1). All individuals were of known age, except for 14 bonobos and 12 chimpanzees for whom an estimated age was taken from the studbook. The protocol of sample collection was approved by the authorities of each zoo.

Urine samples were collected throughout the day (07:00 to 16:00 h) and the time of day, date, and identification of the individual was written on the sample tube. Samples were either collected in plastic tubes directly from the urine stream or taken off the ground with disposable plastic pipettes by zoo keepers. Samples were only collected when the individual could be identified and when contamination with feces could be excluded. After collection, the samples were stored at – 20 °C and transported frozen to the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany. Total T3 was measured with a total T3 ELISA, which was validated during this study for bonobo and chimpanzee urine (Appendix Materials and methods A.1). To compensate for variation in volume and concentration of the urine, we measured specific gravity (SG) with a digital handheld refractometer (TEC, Ober-Ramstadt, Germany) and calculated the TT3 corrected for SG as described in Miller et al. (2004).

Table 1
Number of bonobos and chimpanzees per age category for urinary total T3 measurements.

Age category	Bonobo			Chimpanzee		
	Male	Female	Age estimated[a]	Male	Female	Age estimated[a]
1–5 years	8	8	–	3	4	–
6–10 years	8	10	–	8	8	–
11–15 years	8	9	–	9	9	–
16–20 years	4	8	2	4	10	–
21–30 years	14	9	6	4	15	6
>30 years	2	8	6	7	19	6

[a] Number of individuals in which age was estimated.

Statistical analyses

To explore differences in TT3 concentrations in bonobo and chimpanzee urine samples, we ran general linear mixed models (GLMM, Baayen, 2008). All models were conducted using R (R Core Team, 2012) with the function lmer provided by the package lme4 (Bates et al., 2012). For all models, we tested underlying assumptions (e.g., normal distribution and homogeneity of residuals) by visual inspection of histograms, a qq-plot of the residuals, and by plotting residuals against fitted values. In each case, we found that no assumption was violated (Appendix Materials and methods A.1).

To investigate the influence of the predictor variables (a) sex, (b) age, and (c) sampling time (predictors with fixed effects) on TT3 corrected for specific gravity (SG) (TT3 corrected for SG was the log-transformed response variable) in bonobos and chimpanzees we used GLMMs into which we included in addition to each of the main effects an interaction between sex and age. Furthermore, we included location (zoo) and chimpanzee status (on contraception, castration or sterilization) as random effects. To achieve comparable estimates, time of sample collection and age of the animal were z-transformed to a mean of zero and a standard deviation of one (Schielzeth, 2010).

To establish the significance of the fixed effects as a whole, we compared the full model with a null model excluding all fixed effects but retaining the random effects using a likelihood ratio test (Dobson, 2008; R function 'ANOVA'). In order to achieve reliable *P*-values for the individual effects, we used Markov chain Monte Carlo (MCMC) sampling to establish significance (Baayen, 2008) using the functions pvals.fnc as provided by the R package languageR.

To test for the timing of decreasing TT3 levels (corrected for SG) in both species, we assigned individuals to age categories as described above and treated age as a categorical predictor. We then ran the same model as described before. We changed the reference category of the factor age and ran the model repeatedly to assure that each age category was compared with all others.

Results

Age related changes in TT3 levels

To investigate the possible influence of age and sex on TT3 concentration in urine samples, we compared the full model with a null model for TT3 in both species. This comparison revealed significant effects for each species ($TT3_{bonobo}$: $P_{MCMC} < 0.001$, $TT3_{chimpanzee}$: $P_{MCMC} = 0.024$). The initial models showed that the two-way interactions for sex and age were not significant ($TT3_{bonobo}$: $P_{MCMC} = 0.271$, $TT3_{chimpanzee}$: $P_{MCMC} = 0.867$) and therefore, they were removed from both models before running them again without an interaction. Each of the two reduced models showed a significant age effect: in both species TT3 decreases with age (Table 2). In bonobos, males had higher TT3 levels than females, but there was no significant sex difference in TT3 levels in chimpanzees (Table 2).

Table 2
Results of the two reduced general linear mixed models (without interaction of age and sex) investigating age-related changes in total T3 levels in bonobos and chimpanzees ($N_{bonobo} = 96$, $N_{chimpanzee} = 100$).

Term	Estimate	Std. error	P_{MCMC}[a]
Bonobo			
Intercept	0.626		
Sex	0.462	0.146	0.009
Age of individual	−0.174	0.076	0.001
Time of day	0.020	0.073	0.440
Chimpanzee			
Intercept	0.933		
Sex	0.155	0.119	0.134
Age of individual	−0.166	0.059	0.002
Time of day	−0.082	0.062	0.266

[a] MCMC = Markov chain Monte Carlo.

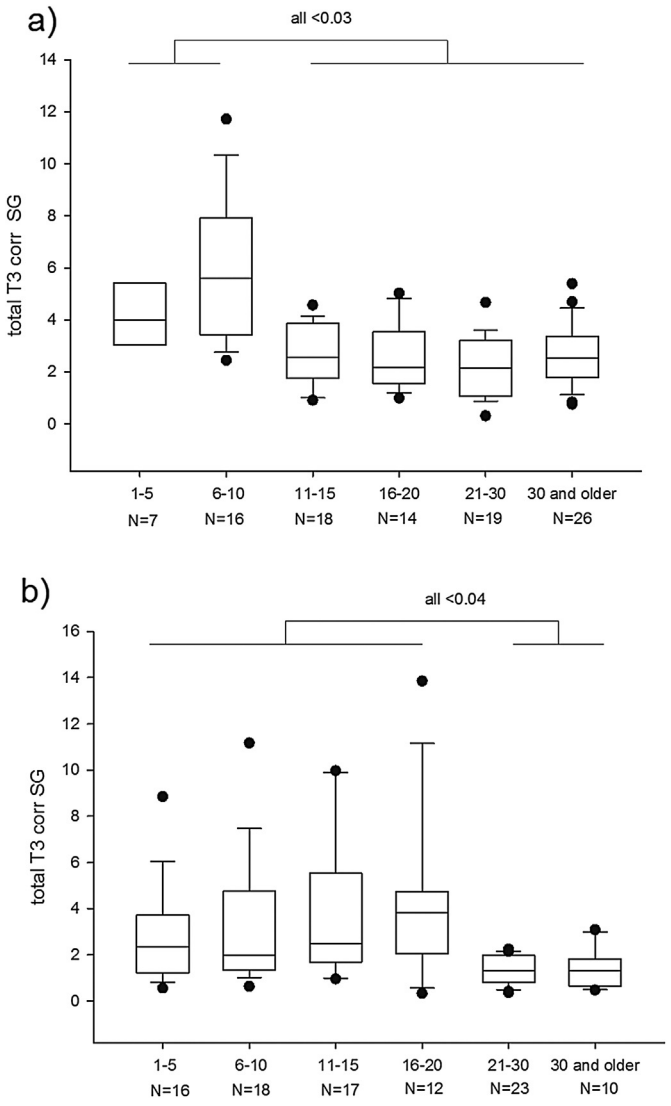

Figure 1. Average total T3 (TT3) concentrations corrected for specific gravity (SG) in urine samples of chimpanzees (a) and bonobos (b) across different age classes (in years). *P*-values are results of posthoc comparisons of urinary TT3 levels of the different age classes. The *x*-axes show age classes and the number of individuals per age class. The boxes indicate the 25th and 75th percentiles, the whiskers indicate the 10th and 90th percentiles, the bars indicate the range, and the circles indicate outliers.

As TT3 was found to decrease significantly with age in both species, subjects were assigned to age classes as has been done in previous studies (Rubenstein et al., 1973). Figure 1 shows that in both species urinary TT3 levels of immatures were higher than in adults. Differences between the two species were found with regard to the timing of the decline in urinary TT3. In chimpanzees, TT3 values declined significantly between age class 6–10 years and age class 11–15 years (Fig. 1a). In bonobos, TT3 values only decreased significantly between age class 16–20 years and age class 21–30 years (Fig. 1b).

Discussion

The temporal variation in TT3 observed in bonobos and chimpanzees corresponds to the pattern that has been found in humans

(Rubenstein et al., 1973; Hesch et al., 1977), with high thyroid hormone levels in immature individuals and a marked decrease in thyroid hormone levels with age. The two species differed in terms of the timing of the decrease, however, with chimpanzees experiencing a significant decrease in TT3 levels several years earlier than bonobos. Human studies indicate considerable variation in the age at which thyroid hormone levels decline, with values ranging between five and 12 years (Table A.2), which complicates direct comparison between *Homo* and *Pan* species. Nevertheless, it is obvious that the decline of TT3 in chimpanzees falls within the range of humans (eight to ten years of age) while TT3 values in bonobos decrease years later (after 20 years of age).

Given the consistent difference between natural and captive environments, and its impact on ontogeny, it is obvious that information obtained from subjects living in captivity may not necessarily be representative of information obtained from conspecifics living in a natural environment (Muller and Wrangham, 2005). Although the comparison of the data from the two *Pan* species with data from western human populations might reduce the effect of divergent ecologies, we are well aware that corresponding information from wild bonobos and chimpanzees is required before drawing any major conclusion concerning the temporal asymmetry in urinary thyroid hormone levels.

Since the urine samples contain a metabolite of the circulating thyroid hormones, we cannot exclude the possibility that the temporal asymmetry in TT3 decline reflects inter-specific differences in age-dependent metabolism of thyroid hormones. To put this into perspective, we can compare our results with studies of other developmental markers in the two *Pan* species. Asymmetries in the emergence of morphological and behavioral traits have been reported in a number of previous studies (Shea, 1988; Kuroda, 1989; De Lathouwers and Van Elsacker, 2006; Wobber et al., 2010a; Durrleman et al., 2012) and most of them conclude that development in bonobos is delayed when compared with chimpanzees. For example, the two species have been found to differ in a number of parameters such as cranial morphology, body size, and growth patterns, with bonobos retaining juvenile traits into adulthood. In bonobos and chimpanzees, the rate of increase in somatic growth (body size and weight) reaches a peak between seven and ten years and declines thereafter (Leigh and Shea, 1996). The retention of juvenile characteristics by adult individuals, or neoteny (Lorenz, 1971), is associated with retardation in somatic growth or early termination of maturation (Gould, 1977). Given the link between somatic growth and thyroid hormone levels, this matches well with the maximum TT3 levels found in the samples from chimpanzees. However, in bonobos, this age-related symmetry does not hold as the timing of the decline in TT3 occurs years after somatic growth has ended.

Closely related species living in different habitats have been found to differ in terms of thyroid hormone levels and/or thyroid hormone secretion patterns (Kitano et al., 2010). The argument is that successful occupation of new habitats depends on elevated stress resistance as founder populations are expected to recruit stress tolerant individuals that, in turn, are characterized by a specific thyroid rhythm (Crockford, 2002). This can ultimately lead to new phenotypes or speciation (Crockford, 2006). The evolution of the two *Pan* species has been linked to geographic separation and it is assumed that the split of the ancestral population happened when bonobos colonized the forest south of the Congo river, a habitat characterized by reduced seasonality and relatively high resource abundance (Wrangham and Peterson, 1996). Based on this scenario, we would expect to find thyroid hormone levels differences in the two *Pan* species. While this interpretation is in line with the observed differentiation in thyroid statuses in geographically separated populations or sub-species of other taxa (Crockford, 2002, 2006), it does not explain the extended period of elevated urinary TT3 levels found in bonobos.

Endocrine systems are affected by aging, and data from humans show that the decrease in thyroid hormone levels observed during aging is due to lower levels of thyroid stimulating hormone (TSH) in serum (Larsen and Ingbar, 1992; Suzuki et al., 2012). In orangutans, TSH values show the same trend with older subjects having lower values than young ones (Maggioncalda et al., 2000). Although nothing is known about age-related changes in TSH in the two *Pan* species, a few studies on aging patterns in hominoid primates have been undertaken. In a comprehensive review, Erwin and Hof (2002) present data suggesting that female bonobos are more likely to reach menopause than female chimpanzees but it remains unknown if this is due to earlier reproductive senescence or increased longevity in female bonobos. However, a recent survival analysis of captive *Pan* species indicates that the survival rate of female bonobos is indeed significantly higher than that of female chimpanzees (Schubert, 2010). As life history theory predicts that long life expectancy delays maturation (Barrickman et al., 2008), the relatively late decline in bonobo urinary TT3 would correspond well with an extended life expectancy in bonobos.

Thyroid hormone levels affect various behavioral patterns, including agonistic behavior (Crockford, 2002; Trut et al., 2004). There are marked differences in the social behavior of the two *Pan* species, and one that has gained particular attention is the low intensity of aggression in male bonobos (Wrangham and Peterson, 1996). It has been proposed that high food abundance and reduced mate competition diminished the advantages from aggressive behavior and, as a result, that selection may have favored docile behavior and non-aggressive competitions (Surbeck et al., 2011; Hare et al., 2012). Aggression and violence are linked to stress and many studies have shown a temporal correlation between stress and aggressive behavior (Barnett et al., 1991). Behavioral responses to stress are influenced by the production of adrenal hormones that are controlled by adrenal receptors whose activity is affected by thyroid hormone levels (Schreibman et al., 1993). Therefore, thyroid hormones may influence behavioral responses to stress, including aggressive behavior, as has been shown empirically in humans, dogs, and rodents. In humans, there is a negative correlation between aggressiveness and T3/T4 ratio (Sinai et al., 2009) and in domestic dogs intense aggression coincides with hypothyroidism and can be reduced to normal levels with the administration of thyroid hormones (Miklósi, 2007). In the context of our study species, the relationship between aggression and thyroid hormones remains to be explored and species-differences in thyroid hormone levels of adult individuals may lack a generalized behavioral equivalent. However, in light of the consistent between-species differences in the intensity of aggressive behavior (lethal versus non-lethal aggression) on the one hand, and the proposed effect of thyroid hormone levels for speciation (Crockford, 2010) on the other, it would be premature to exclude variation in thyroid hormone activity as a force promoting the divergent evolution of *Pan* species (Hare et al., 2012).

In bonobos and chimpanzees, there is considerable inter-individual variation in aggressive behavior that can be linked to male dominance and it has been shown that the changes in behavior correlate with urinary testosterone and cortisol levels (e.g., Surbeck et al., 2012). The data on thyroid hormone levels in the two *Pan* species add novel information that needs to be fully integrated into the ontogenetic endocrinology of bonobos and chimpanzees. Using urine as a matrix for thyroid hormone extraction can also be applied in studies of wild animals as urine storage for extraction of other hormones from wild animals has already proved successful. Endocrine parameters of growth control

and behavioral maturation offer a promising tool to further explore the timing and magnitude of behavioral changes in hominoid primates and to understand ontogeny and life history parameters of our closest living relatives.

Conclusion

Analyses of total T3 (TT3) in urine samples of the two *Pan* species revealed temporal variation in TT3 levels. In both species, immatures had higher values than adults. Chimpanzees experienced a significant decrease in TT3 levels years earlier than bonobos. This pattern of changing TT3 levels corresponds with the developmental delay in bonobos and the reduced aggression in adult male individuals.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jhevol.2013.09.008.

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