Original Research Article

Ontogenetic Changes in Cranial Vault Thickness in a Modern Sample of *Homo sapiens*

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Objectives: This work assesses cranial vault thickness (CVT) ontogenetic changes using a computed tomography database to register thickness across multiple regions.

Methods: Vault images of 143 individuals from 0 to 31 years old were analyzed by thickness semiautomatic measurements. For each individual, we obtained a thickness mean measure (TMM) and its coefficient of variation, a measure of endocranial volume (EV), the distribution of relative frequencies of thickness—relative frequency polygon, and a topographic mapping that shows the thickness arrangement through a chromatic scale. Ontogenetic changes of these variables were evaluated by different regression models (TMM vs. age, EV vs. age, TMM vs. EV) and visual comparisons between the age groups.

Results: TMM increased during ontogeny until the onset of adulthood without sex differences, but the most accelerated growth rates occur during the first 6 years of postnatal life. TMM variations were associated with EV only in infants and children, but not in later periods. The polygons showed a flattening during ontogeny, probably due to an increase in thickness variation within individuals. However, the adult pattern of thickness arrangement, with the lateral region thinner than the regions near sagittal plane, was detected from infancy.

Conclusion: The pattern of thickness arrangement is established early in ontogeny but CVT increases and changes in distribution until adolescence. Several factors may influence CVT, such as the brain, muscles, vessels, and sutures. Am. J. Hum. Biol. 00:000–000, 2014.

Cranial vault thickness (CVT), defined as the distance between the inner (endocranium) and the outer (ectocranium) surfaces of vault bones, is a widely studied variable in physical anthropology. Significant differences in CVT have been found between hominin species (Balzeau, 2013; Copes, 2011; Gauld, 1996; Howells, 1966; Kennedy, 1991; Nawrocki, 1991; Weidenreich, 1943; Wolpoff, 1980) and even among modern human populations (Curnoe, 2009; Marsh, 2013). At an ontogenetic scale, CVT shows important changes as bones develop and different morphogenetic processes take place.

Many studies have pointed out that CVT is not strongly genetically determined, but epigenetic responses to systemic and regional stimuli would play a key role in CVT development (Baab et al., 2010; Lieberman, 1996; Menegaz et al., 2010). It is generally believed that CVT, as other morphological traits of the vault, depends on the variation of functional matrices, such as brain and muscles that are associated with bone structures (Moss and Young, 1960; Opperman et al., 2005; Sperber, 2010).

The brain is thought to be the organ that most importantly affects vault morphology (Moss and Young, 1960; Richtsmeier et al., 2006). It exhibits an early development with a marked increase in size during the first 3 years of postnatal life. Then, it decelerates its growth rates and grows slightly after deciduous dentition is completed (Giedd et al., 2009; Guihard-Costa and Ramírez Rozzi, 2004; Lenroot and Giedd, 2006; Ventrice, 2011). The endocranial volume (EV), which is a good proxy of brain size, achieves 90–95% of adult size around 7–8 years old (Neubauer et al., 2009; Ventrice, 2011). Tensional forces promoted by the brain stimulate osteogenetic activity on sutures, influencing their patency and, therefore, overall skull shape (Opperman et al., 2005). Shape changes of the vault related to brain ontogeny involve antero-posterior elongation, relative narrowing, shortening of the distance between bregma and vertex, and compression of the parietal superior area (Enlow and Hans, 1996; Moss, 1962; Moss and Young, 1960; Opperman et al., 2005; Sperber, 2010; Ventrice, 2011; Barbeito-Andrés et al., 2015). The influence of the growing brain on bones has been also demonstrated by the study of certain pathologies such as anencephaly (Dambska et al., 2003; Frey and Hauser, 2003; Zhao et al., 1996), hydrocephaly (Morimoto et al., 2003), microcephaly (Chervenak et al., 1984), and craniosynostosis (premature closure of cranial sutures) (Richtsmeier et al., 2006).

It has also been proposed that masticatory and nuchal muscles influence skull morphology and CVT. After the eruption of the deciduous first molar, masticatory muscles grow significantly as they become increasingly involved in chewing (Sperber, 2010) and the pubertal spurt drives sexual dimorphism in muscular size (Raadsheer et al., 1996). Experimental studies conducted on different mammals demonstrated that muscular contraction stimulates

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osteogenetic activity (Herring, 1993; Herring and Teng, 2000). In nonhuman primates, well-developed muscles exert large forces on the ectocranial surface and have been linked to the development of crests and superstructures (Goswami and Polly, 2010). However, masticatory muscles are relatively thin in humans (Aiello and Dean, 2002; Stedman et al., 2004) and their impact on vault morphology may be negligible compared to the forces exerted by the brain (Cheverud, 1996; Enlow and Hans, 1996; Moss and Young, 1960).

The developmental bases of CVT remain scarcely known. Around birth bones present a unilaminar configuration. Later, the inner and outer tables differentiate because the diploe develops between them (Sicher and DuBrul, 1970). Although some studies have indicated that CVT increases until adulthood (Adeloye et al., 1975; Gauld, 1996; Roche, 1953; Todd, 1924), contrasting results were obtained by Lynnerup (2001) and Lynnerup et al. (2005), who did not detect correlations in CVT and diploe thickness with age. Bone growth is also mediated by circulating hormone levels; for instance, growth hormone (GH) is supposed to interact with CVT because acromegalic patients (high levels of GH) and individuals with hypopituitarism (low levels of GH) have significantly thicker and thinner cranial vaults, respectively, than normal individuals (Copes, 2011; Randall, 1989). Lieberman (1996) observed that physical exercise was directly correlated with CVT in pigs. Physical activity would increase the levels of GH, and these levels would explain the different thickness observed between exercised and not exercised individuals (Lieberman, 1996). However, experimental studies that specifically measured circulating hormone concentration in female mices found that CVT does not relate significantly to hormone levels or physical activity (Copes, 2011).

Regarding sexual dimorphism, some studies observed that adult males and females do not have significant differences in CVT (Lynnerup, 2001; Lynnerup et al., 2005; Nawrocki, 1991; Ross et al., 1998). Other studies have reported that the sexes differ in the CVT of some particular vault regions (Hatipoglu et al., 2008; Marsh, 2013; Moreira-Gonzalez et al., 2006). In general, males show a thick posterior vault, mainly in the occipital region, while females display a thick anterior vault (Axelsson et al., 2003; Ebraheim et al., 1996; Hwang et al., 2000; Lynnerup et al., 2005; Roche, 1953). In contrast to this widely accepted pattern, Copes (2009) found that the thickest regions are located at the frontal and occipital bones in males and at the parietal and occipital bones in females. Marsh (2013), instead, identified another pattern, in which males present thicker sagittal regions, although this difference is not statistically significant.

These incompatible results may be due to the difficulty of getting access to the endocranial surface. In some cases, CVT has been measured at single points where the caliper arm reaches the endocranial surface (Twiesselmann, 1941). Through the use of hemisected vaults, it was possible to describe both surfaces without being limited to the inspection of specific points (Moreira-Gonzalez et al., 2006), but this strategy implies the destruction of bone material. Radiographs have become a useful tool to quantify bone thickness and to avoid bone destruction, although quantification is restricted to few planes of measurement (Adeloye et al., 1975; Brown et al., 1979; Jacobsen et al., 2008; Roche, 1953; Smith et al., 1985).

In most of these studies, CVT was assessed using landmarks placed on sutural intersections, known as Type I landmarks (Bookstein, 1991). These landmarks are homologous and easily identifiable in different individuals (Bookstein, 1991). However, their localization may change across ontogeny in relation to the closure of the sutures (Barbeito-Andrés et al., 2012). It has also been proposed to take thickness measurements at arbitrarily selected points defined by a distance to Type I landmarks (e.g., 3 cm anterior to the bregma; Adeloye et al., 1975). Nevertheless, this kind of measurement may bias variation between individuals in the thickness value.

Recently, CVT studies with computed tomography (CT) images have been applied (Balzeau, 2013). The study of CT facilitated the analysis of internal structures without bone destruction and, as it enables the semiautomatic and simultaneous measure of vault thickness over multiple points, it became possible to obtain a topographic mapping of vault thickness (Balzeau, 2013). In this work, we used a cross-sectional CT database of human individuals and obtained a topographic mapping of CVT in each vault with the purpose of assessing variation in CVT from birth to adulthood. Different measures of variation within and among individuals were carried out to test the following hypothesis:

Hypothesis 1 (H1): CVT increases with age. As the vault is affected by developmental factors with the systemic effect of promoting somatic and skeletal growth, we expect that CVT increases with age, as was suggested by some previous studies (e.g., Adeloye et al., 1975; Gauld, 1996; Roche, 1953; Todd, 1924). As for other cranial traits males and females differ in ontogenetic trajectories (Anzelmo et al., 2012; Strand-Vidarsdottir and O'Higgins, 2001; Ventrice, 2011), it is additionally expected that ontogenetic changes of vault thickness differ between sexes.

Hypothesis 2 (H2): CVT changes are associated with EV changes. EV changes with age as the brain grows because the brain is an important factor influencing vault morphology, it is expected that ontogenetic changes in EV are associated with CVT variation.

Hypothesis 3 (H3): The pattern of CVT distribution and arrangement changes during ontogeny. Because the vault is affected by several developmental factors, mainly by functional matrices (e.g., brain, muscles, vessels, etc.; Moss and Young, 1960), which grow with different rates and at different moments, regional variation in thickness within individuals and a change in its arrangement (i.e., the topographic thickness mapping) with age is expected.

CVT is among those morphological traits that show important variation between different hominins and among modern humans (Balzeau, 2013; Copes, 2011; Gauld, 1996; Howells, 1966; Kennedy, 1991; Marsh, 2013; Nawrocki, 1991; Weidenreich, 1943; Wolpoff et al., 1984). Additionally, the vault is a preferred structure from which to obtain bone grafts for medical purposes, which are extracted from the thickest regions (Elahi et al., 1997). The thinnest and thickest vault regions have been studied among adults, but little is known about the thickness arrangement in subadults. Comprehensive knowledge about the ontogenetic changes of CVT can be useful to define possible developmental factors responsible for its

variability that could be involved in the generation of phylogenetic differences. As well as to define the developmental moment when the adult pattern of thickness arrangement is established to assist surgeons when choosing an area of cranial bone graft harvesting in pediatric surgery.

MATERIALS

In this work, we used a sample of 143 CT cranial images obtained from Fundación para la Lucha contra las Enfermedades Neurológicas de la Infancia (Buenos Aires, Argentina). These CT images were obtained because patients showed some clinical signs with a potential neurological basis. The database comprises males and females, ranging from 0 to 31 years old, in which no neurological pathologies were detected. Most of the individuals came from Buenos Aires and cities surrounding Buenos Aires; a minor proportion came from other Argentinean regions.

Because infant, child, juvenile, and younger adolescent individuals have a reduced bone thickness, they were scanned with a specific protocol with less exposure to X-ray (Protocol 1) while older adolescents and adults were scanned with a different protocol (Protocol 2). Protocol 1 was performed as follows: scanned in axial mode, 150 mA1 of current, 120 kVp2 of accelerating voltage, and a gantry/detector tilt positioned in 0.0° that produced 208–304 axial CT images (resolution: 512 × 512 pixel) depending on individual, with a voxel size equal to 0.449 × 0.449 × 0.625 mm shared by all the individuals. Protocol 2 was performed as follows: scanned in axial mode, 200 mA, 120 kVp, gantry/detector tilt position at 0.0° which gave 240–304 axial CT images (resolution: 512 × 512 pixel) depending on individual, with a voxel size equal to 0.449 × 0.449 × 0.625 mm shared by all individuals. CT images of each individual were transformed from Digital Imaging and Communications in Medicine format to analyze format for compatibility reasons; during this procedure images became anonymous using the program Medical Image Processing, Analysis and Visualization (MIPAV) (McAuliffe et al., 2001).

To make some analyses, the sample was divided into age groups according to stages of the life cycle postulated by Bogin (1999) (Table 1). The divisions are based on several traits of body and behavioral maturation, such as brain growth, dental eruption, and sexual and cognitive development. Bogin (1999) distinguishes infants (0–2 years old) and children (3–6 years old). As infants are few in number, they were pooled together with children for statistical analyses. The juvenile period ranges from 7 to 11 years old. The adolescent period ranges from 12 to 17 years old, and adulthood includes all individuals over 17 years old.

TABLE 1. Sample size by age groups and sex

Age groups (years)	Males	Females	Total
Infant–Child (0–6)	10	7	11
Juvenile (7–11)	16	10	26
Adolescent (12–17)	13	16	29
Adult (+17)	19	52	71
Total	58	85	143

METHODS

Cranial images were imported and analyzed with Avizo 6.0 (Science Visualization Group). From CT slices of each individual, a 3D skull was reconstructed. These reconstructions were performed through a segmentation technique that differentiates the head tissues by threshold values. Each threshold represents the minimal intensity of a given tissue and is expressed in Hounsfield units (Spoor et al., 2000). Once the bone minimal intensity was detected, the every pixel with a larger intensity value was selected to segment bone. The appropriate threshold value was determined empirically. A threshold of 1,150 Hounsfield units was chosen to show the maximum amount of bony tissue with the least amount of distortion in individuals of different ages.

To obtain a measure of EV, the 3D endocranial cavity was reconstructed from the segmented endocranial surface, and a value of EV for each individual was obtained.

The vault was separated from the facial skeleton and the basicranium using MIPAV software (McAuliffe et al., 2001). The slice delimiting the vault was defined by three landmarks: glabella, right asterion, and left asterion. All slices above this plane were retained. The resulting vault reconstruction was created with Avizo.

First, all structures localized between endocranial and ectocranial surface, for example, the frontal sinus, were eliminated because these structures may bias thickness measures. Second, bone thickness was calculated with the Surface Thickness module of Avizo program that computes the thickness as the shortest distance of each vertex in the direction of its normal with all the triangles of the same material. Through this procedure, a thickness measure for each vertex was obtained. A 3D topographic mapping indicating bone thickness variation at different vault regions was obtained and rendered with a chromatic scale. For each individual topographic mapping, we obtained: (1) a thickness mean measure (TMM) and a standard deviation for the entire vault and (2) a relative frequency polygon with classes of 0.5 mm that shows the distribution of bone thickness values.

The first hypothesis was tested by means of different methods. To evaluate variation between individuals of different age, the ontogenetic trajectory of TMM was depicted. First, whether or not sex is a factor influencing the trajectory was assessed. This was evaluated by a regression analysis for each ontogenetic group with TMM as a dependent variable, age as an independent variable, and sex as a categorical variable. By means of this analysis, the interaction term (age*sex) enabled the detection of significant changes in the slopes of regression lines between the sexes. If the slopes of males and females did not differ, further analyses were performed pooling the sexes together.

Second, a linear regression analysis within each ontogenetic group was carried out using TMM as a dependent variable and age as an independent variable to evaluate growth rates of CVT. Third, to detect changes in growth rates between contiguous ontogenetic groups, a further regression was done adding the ontogenetic groups as a categorical variable. The interaction term (age*ontogenetic group) enabled the assessment of significant changes in the slopes of regression lines between contiguous groups.

As EV represents a size measurement that may be developmentally related with TMM, all these procedures

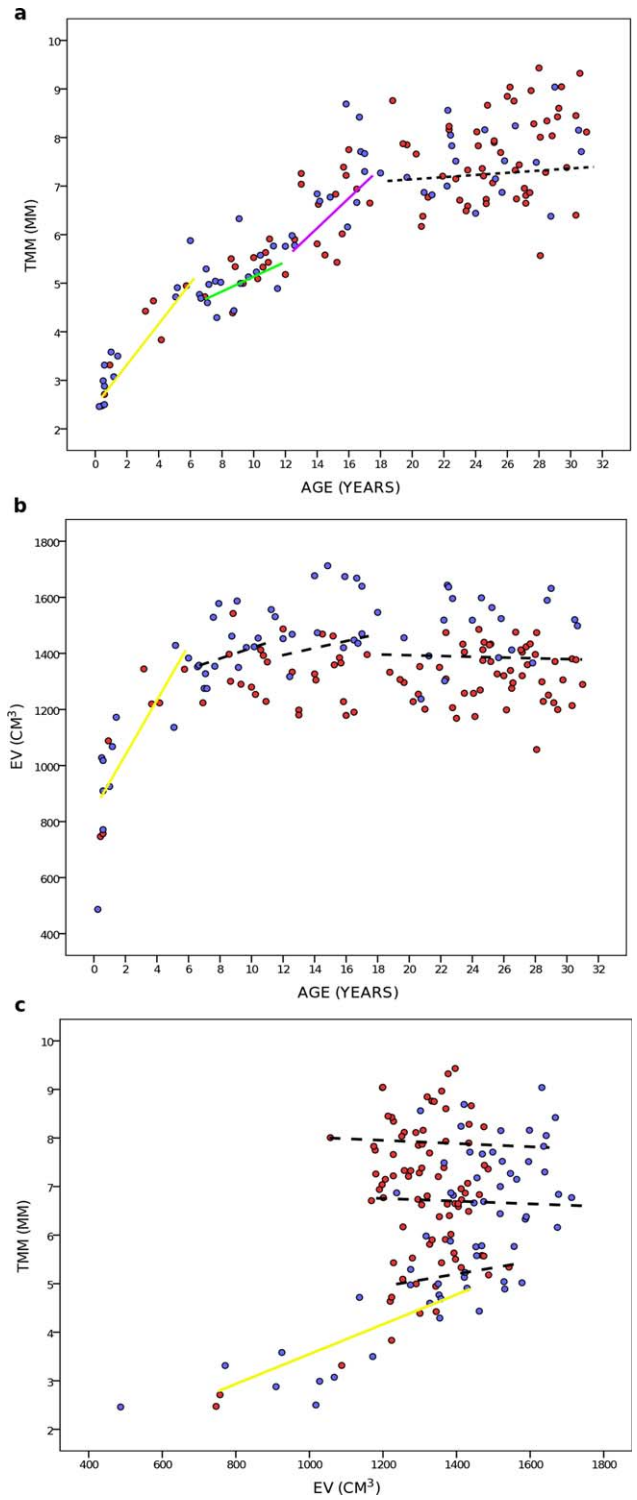

Fig. 1. Distribution of males (blue) and females (red) according to (a) age versus TMM; (b) age versus EV; and (c) EV versus TMM. Regression lines pooling sexes are shown for infant-childhood (yellow), juvenile (green), and adolescent (violet). Nonsignificant regression lines are shown as dotted lines.

were performed with EV and age, and EV and TMM. In this last case, EV was the independent variable. These analyses were useful to evaluate H2.

TABLE 2. Slope values of regression analyses for TMM and EV versus age using sex as categorical variable

	TMM			EV		
	R^2	F	P	R^2	F	P
Infant–child	0.888	0.259	0.618	0.649	0.123	0.731
Juvenile	0.308	0.429	0.519	0.349	1.260	0.273
Adolescent	0.407	1.101	0.304	0.476	0.979	0.332
Adult	0.068	0.068	0.795	0.381	0.342	0.560

R^2: Coefficient of determination.

To explore the variation within individuals in CVT and the ontogenetic changes in variation, the relative frequency polygons were depicted along a common scale. The shape of a polygon is considered an indicator of individual variation. Within-individual variation along ontogeny was additionally evaluated by the coefficient of variation (CV). This enabled the assessment of whether variation was scaled to the mean.

Finally, thickness arrangement variation between different age groups was tested through a visual comparison of the 3D topographic mapping. All individuals were analyzed, but here, we show a randomly selected sample comprising four individuals, two males, and two females, from each group. First, vault thickness arrangement was displayed by a common chromatic scale for different individuals. This enabled the assessment of changes in variation between regions during ontogeny. This common scale extends from 1.5 to 11.5 mm and each interval of 2 mm was represented with different contrasting colors to highlight variations in topographic mappings. Second, a particular chromatic scale was used for each individual to assess variation in the thickness arrangement pattern during ontogeny. The particular scale represents thickness classes with frequencies greater than 5%, and it is composed by the same color for different individuals.

The relative frequency polygons and topographic mappings allowed for the assessment of H3.

RESULTS

Changes in TMM and EV against age are shown in Figure 1a, b, respectively. Regression analyses using sex as a categorical variable showed that slopes do not differ between males and females in any ontogenetic stage (Table 2). As slopes of TMM and EV did not differ, the sexes were pooled together in the following analysis.

The regression analyses indicated that within each ontogenetic stage, CVT changes were significant until adolescence but not during the adult stage (Table 3, Fig. 1a). The evaluation of growth rate variation during ontogeny, analyzed by means of a regression analysis using contiguous age groups as a categorical variable, demonstrated that significant changes in slopes occurred between infant/child and juvenile groups and between adolescents and adults, but nonsignificant differences between juveniles and adolescents were obtained (Table 4, Fig. 1a).

According to these results, three ontogenetic periods with different rates of CVT growth can be differentiated (Fig. 1a). Important rates of change were detected in the infant/childhood group, mainly during the first 2 years of postnatal life. Thereafter, rates decelerated and then slowed down in adulthood (Fig. 1a). Males and females overlapped their distribution along the trajectory (Fig. 1a).

TABLE 3. Slope values of regression analyses for TMM and EV versus age and allometric relation

	TMM vs. AGE			EV vs. AGE			TMM vs. EV		
Age group	R^2	F	P	R^2	F	P	R^2	F	P
Infant–child	0.881	118.65	0.0001[b]	0.646	29.183	0.0001[b]	0.653	32.941	0.0001[b]
Juvenile	0.294	10.435	0.003[b]	0.047	1.239	0.276	0.101	2.802	0.106
Adolescent	0.342	13.488	0.001[b]	0.029	0.778	0.386	0.0001	0.0001	0.999
Adult	0.066	0.278	0.602	0.001	0.048	0.828	0.011	0.763	0.385

R^2: Coefficient of determination.
[a]probability < 0.05.
[b]probability < 0.01.

TABLE 4. Slope values of regression analyses for TMM and EV versus age and allometric relation between contiguous ontogenetic groups

	TMM vs. AGE			EV vs. AGE			TMM vs. EV		
Age group	R^2	F	P	R^2	F	P	R^2	F	P
Infant-child/juvenile	0.865	17.771	0.0001[b]	0.734	13.681	0.0006[b]	0.762	4.366	0.049[a]
Juvenile/adolescent	0.702	1.928	0.171	0.046	0.0001	0.985	0.564	0.785	0.379
Adolescent/adult	0.278	6.294	0.013[a]	0.034	1.051	0.307	0.186	0.268	0.606

R^2: Coefficient of determination.
[a]probability < 0.05.
[b]probability < 0.01.

In contrast, EV increased significantly with age during just the first 6 years of life (Table 3, Fig. 1b). The slopes of growth between the infant/child and the juvenile groups differed significantly, but they did not show significant differences between juveniles and adolescents and between adolescents and adults (Table 4, Fig. 1b). Thus, the only change of EV occurred during the first 6 years on life.

Regression analysis within each age group detected a positive allometric relationship during infancy-childhood, but allometric changes were not significant during later ontogeny (Table 3, Fig. 1c). The slopes of growth differed significantly between infant/child and juvenile groups, but they were not significant between juveniles and adolescents, and adolescents and adults (Table 4, Fig. 1c). As shown in Figure 1c, CVT is associated with EV just during the first ontogenetic period considered here.

Ontogenetic changes in the relative frequency distribution are shown in Figure 2. As already mentioned (Fig. 1a), from infancy to adulthood, bones became thicker as the individuals in older groups were displaced to higher values of the scale (Fig. 2). Males and females did not differ in thickness distribution considering modal classes of both sexes in each age group (Fig. 2).

The shape of frequency polygons provided an estimation of variation within individuals. Infants and children spanned a smaller range of thickness classes than adults. During the first 6 years of life, there was an important shift in the shape of frequency polygons. Infants (from birth to 2 years old) have frequency polygons with a narrower shape than children (from 3 to 6 years), which present a shape more similar to juveniles. Classes with frequencies above 5% spanned from 1.75 to 4 mm in infants while in children they spanned from 3 to 6.75, from 3.25 to 7 in juveniles, from 4.5 to 8.5 in adolescents, and from 5.25 to 9.5 in adults (Fig. 2). Toward late ontogeny, the most frequent classes presented higher thickness values, but the thinnest classes were also represented in adults. As a consequence, polygons of adult individuals were flatter than those of subadults.

Contrasting with the already mentioned results, CV did not indicate such increase (Fig. 3). This suggests that within-individual variation in CVT across ontogeny is scaled with respect to TMM.

To visualize the regional variation in CVT and the arrangement of the thickest and thinnest regions across ontogeny, a topographic mapping with a particular chromatic scale for all individuals was first obtained (Fig. 4). Patterns of CVT arrangement were shared by individuals of different ontogenetic groups (Fig. 4a–e). In the frontal bone, the thinnest values were placed at lateral supraocular regions. The posterior border of the frontal, close to the coronal suture, presented the thickest values and the frontal midline also showed high thickness values. On the middle region (temporal and parietal), thickness increased from temporal squamous to the sagittal suture, being the thickest region placed to both sides of the posterior portion of the sagittal suture. However, a thin line, which coincides with the sagittal suture, was observed. Although the lateral wall was the thinnest region, in particular around the pteric region, it exhibited a complex pattern of CVT arrangement. The occipital bone showed the thickest values at the superior portion of the lambdoid suture and along the midline. Both sides of the occipital are thinner than occipital midline. Infants showed some differences with respect to this pattern because the midline regions were thinner along the vault than the lateral walls in relation to open sutures and fontanelles (Fig. 4a).

Topographic mappings using a common chromatic scale for individuals of different ontogenetic groups were second obtained to evaluate changes in thickness differences among vault regions (Fig. 5). Thickness differences between regions increased during ontogeny (Fig. 5a–e). Accordingly, infants showed a topographic mapping that was more homogenous than older age groups, because their vaults were less variable (Fig. 5a).

DISCUSSION AND CONCLUSION

The results of this study indicate that CVT undergoes important changes during postnatal ontogeny, with males

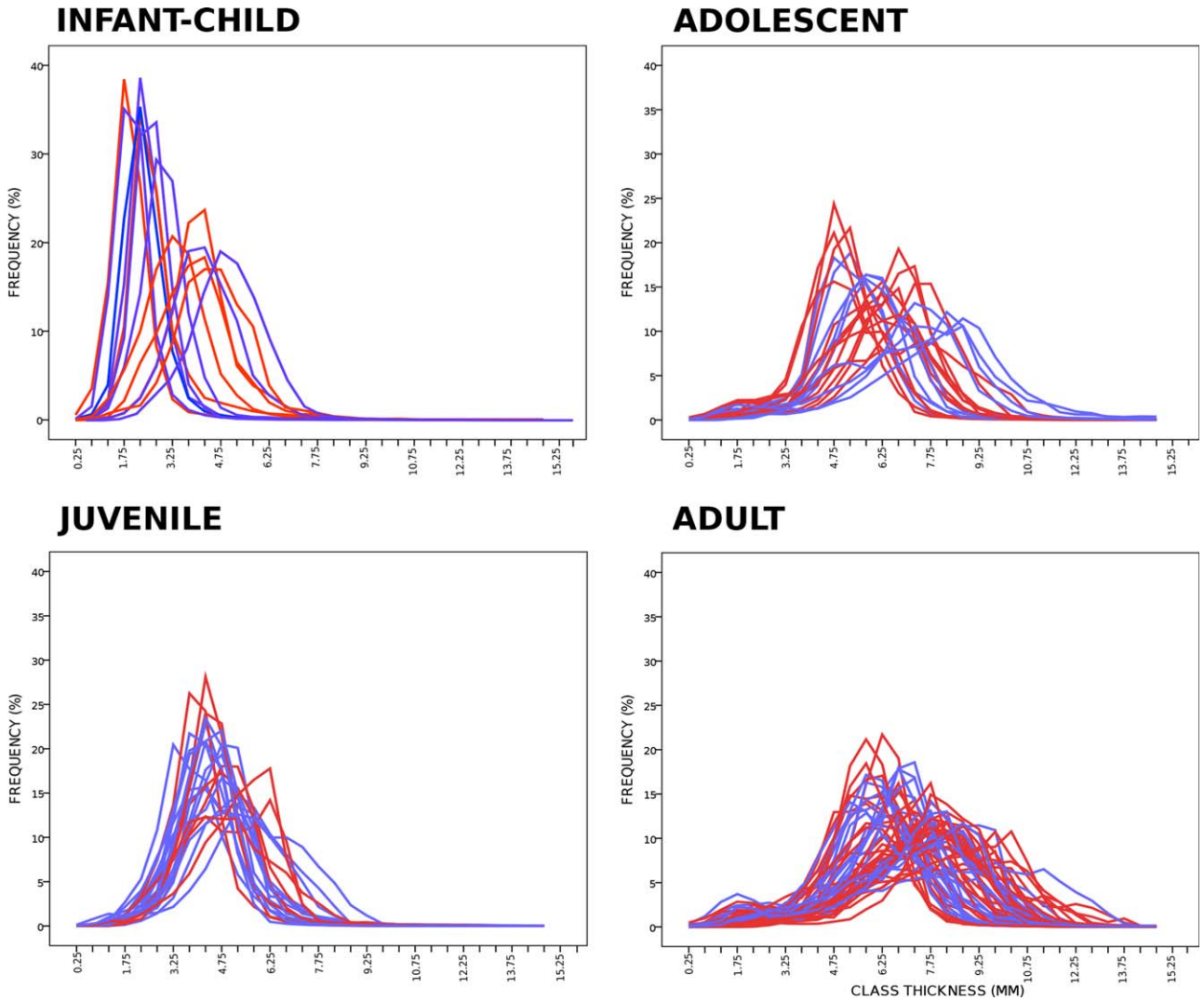

Fig. 2. Relative frequency polygons of individual bone thickness distribution in males (blue) and females (red) by age group.

and females being similar in their ontogenetic changes (Table 2, Figs. 1a and 2). Thickness increases following a nonlinear ontogenetic trajectory (Fig. 1a), which is more pronounced during infancy. Association between thickness and EV provides some clues into the potential influence of the growing brain on CVT. Although results suggest that ontogenetic trajectories of both variables differ (Tables 3 and 4, Fig. 1a, b), during early ontogeny CVT and EV have a steep increase and CVT changes during infant and childhood stages may partly depend on EV increase (Table 3, Fig. 1c). However, endocranial growth ceases during the juvenile period (Tables 3 and 4, Fig. 1b, c) and CVT shows changes until the onset of adulthood (Tables 3 and 4, Figs. 1a, c, and 2).

Relative frequency polygons provided two types of evidence. First, the displacement of older individuals across a common scale expresses that CVT increases during ontogeny, affecting most vault regions. In adults, for instance, the CVT modal classes present higher values than younger individuals (Fig. 2). Second, the change in the shape of relative frequency polygons (Fig. 2)—with a flattening toward the late age groups—would indicate an increase in variation within individuals; CVT values are distributed across a wider range of classes in adult individuals than in the younger groups. However, this result must be considered with caution because the changes in CV did not express such a tendency in internal variation (Fig. 3). This suggests that variation scaled to the mean remains very similar across ontogeny.

Topographic mappings suggest that thickness variation between vault regions within individuals increases during ontogeny (Fig. 5). Adolescents and adults (Fig. 5d, e) demonstrate topographic mapping with more heterogeneity of colors that younger groups (Fig. 5a–c) because more thickness classes of the common scale are represented. However, the pattern of thickness arrangement is similar between individuals of different age stages (Fig. 4). The main characteristics of CVT pattern, focusing on adults (Figs 4e and 5e), can be described as: (1) along the midline, greater thickness detected in the superior glabellar

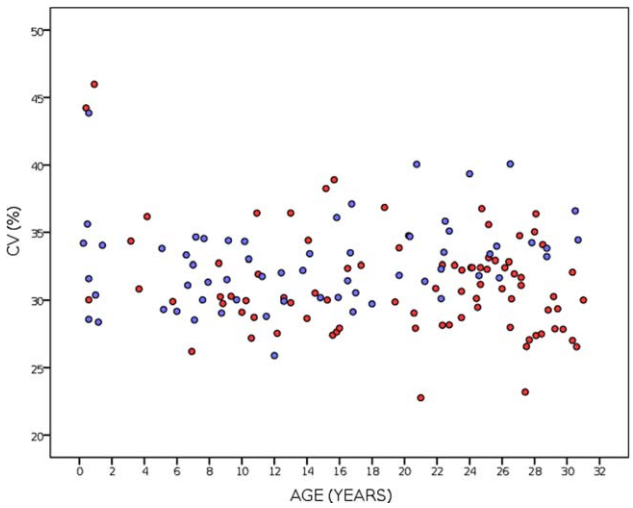

Fig. 3. Distribution of males (blue) and females (red) according to age versus the CV.

region and in the posterior frontal near the coronal suture, to both sides of the sagittal suture in the posterior parietal, and along occipital midline. This pattern is clearly detected from infancy onward; however, infants show the thinnest regions around open sutures and fontanels; (2) the lateral walls are in general thinner that the midline.

Considering overall results, it seems that important changes in CVT occur during early ontogeny. A noteworthy ontogenetic shift in the CVT ontogenetic trajectory occurs at the age of 2 (Fig. 1a) and in the shape of frequency polygons (Fig. 2).

During the first 2 years of life, there are important changes involving the bones of the cranial vault (Baker et al., 2005; Sperber, 2010). To some extent, an increase in thickness can be associated with the general growth in skeletal bone mass due to systemic factors, such as hormones and nutrition (Ballabriga, 2000; Hall, 2005; Lieberman, 1996). Hormonal evidence is contradictory. In the experimental study carried out by Lieberman (1996), an increase of bone thickness throughout the skeleton was detected in those animals that exercised daily. He concluded that this general increase may be a consequence of GH, which induces systematic bone growth. In contrast, Copes (2011) did not find important differences in IGF-1 ratio, used as a proxy of circulating GH, between a group of exercised mice and controls.

Thus, factors with local action can better explain changes in CVT. During the first years of life, the CVT trajectory tracks the growth of the brain, which follows a curvilinear growth path and attains approximately 50% of the adult size by the age of 1 year, 75% by 3 years, and 90% by 7 years (Giedd et al., 2009; Lenroot and Giedd, 2006; Ventrice, 2011). The growing brain exerts mechanical loadings over meningeal layers. These forces are transmitted to osteogenic cells thus influencing the patency of sutures and skull shape (Enlow and Hans, 1996; Moss, 1962; Moss and Young, 1960; Opperman et al., 2005; Sperber, 2010). Due to these high growth rates, some sutures are not already formed (Opperman et al., 2005); however, some bone borders close and all fontanels become closed between 1 and 2 years old (Sperber, 2010). Furthermore, during early ontogeny, vault bones develop a particular histological configuration: inner and outer cortical tables differentiate and acquire a relatively independent behavior due to the development of diploe (Sicher and DuBrul, 1970; Sperber, 2010). These local changes may be an important factor affecting thickness variation. The diploe evolved to adapt bones to brain enlargement. The histological configuration of vault bones acts as a strong barrier protecting the brain where the diploe reduces the weight of the skull without proportionately reducing its strength (Goldsmith, 1972).

Sutures patterning also changes during the first years of life. Once fontanels become fused, osteogenetic activity along sutures is the main mechanism that enables vault expansion. This produces an antero-posterior elongation with the consequent loss of the globular shape that characterizes the newborn. The most active growth site occurs along the lambdoid suture, where growth rate is frequently greater than that of other sutures (Trinkaus and LeMay, 1982). From early ontogeny to adulthood, the regions close to the lambdoid suture are the thickest, but close to the coronal suture the vault remains thin (Figs. 4 and 5). It is thus probable that ossification mechanisms remain active during later ontogenetic stages, mainly near the lambdoid suture, contributing to the development of the increased thickness.

During ontogeny, a pattern of CVT arrangement is evident. As detected in previous works (Laurent et al., 2011; Marsh, 2013), important parts of sagittal plane are thicker than lateral regions, such as posterior frontal, posterior parietals near the sagittal suture, and the occipital bone. Marsh (2013) found that sagittal thickening is a prevalent pattern of thickness arrangement in modern humans. However, along the parietal midline, there is a thin line probably related to the development of the sagittal sinus, which is limited to both sides by thicker regions. The sagittal sinus is an internal depression where meningeal vessels run. The development of this trait can partially explain the pattern observed in the parietal sagittal region.

The thickest region along the midline coincides with the separation between both brain hemispheres. It is likely that the increased thickness along the midline allow bones adapt to empty space between the hemispheres where vessels run and the *falx cerebri* attaches. Previous studies with hydrocephalus individuals demonstrated that when the brain is increased because of abnormal buildup of cerebrospinal fluid in the ventricles, the vault is thin (Morimoto et al., 2003). Conversely, when hydrocephalous children underwent shunting procedures their vault bones become remarkably thick (Moseley et al., 1966) because of the shrinkage of the brain (Anderson et al., 1970; Lucey et al., 2003). It is probable that a similar mechanism could act locally, generating thicker regions where the brain has lower development. The dynamic interactions between CVT and the brain may also explain why some of the thinnest regions of the vault—located in the occipital bone to both sides of the sagittal plane—are the cerebral fossae (Figs. 4 and 5), the development of which follows the protrusion of occipital lobes. In adults, the complex patterning along lateral walls can be related to the development of grooves for meningeal vessels, which contributes to generate an irregular endocranial surface (Figs. 4 and 5).

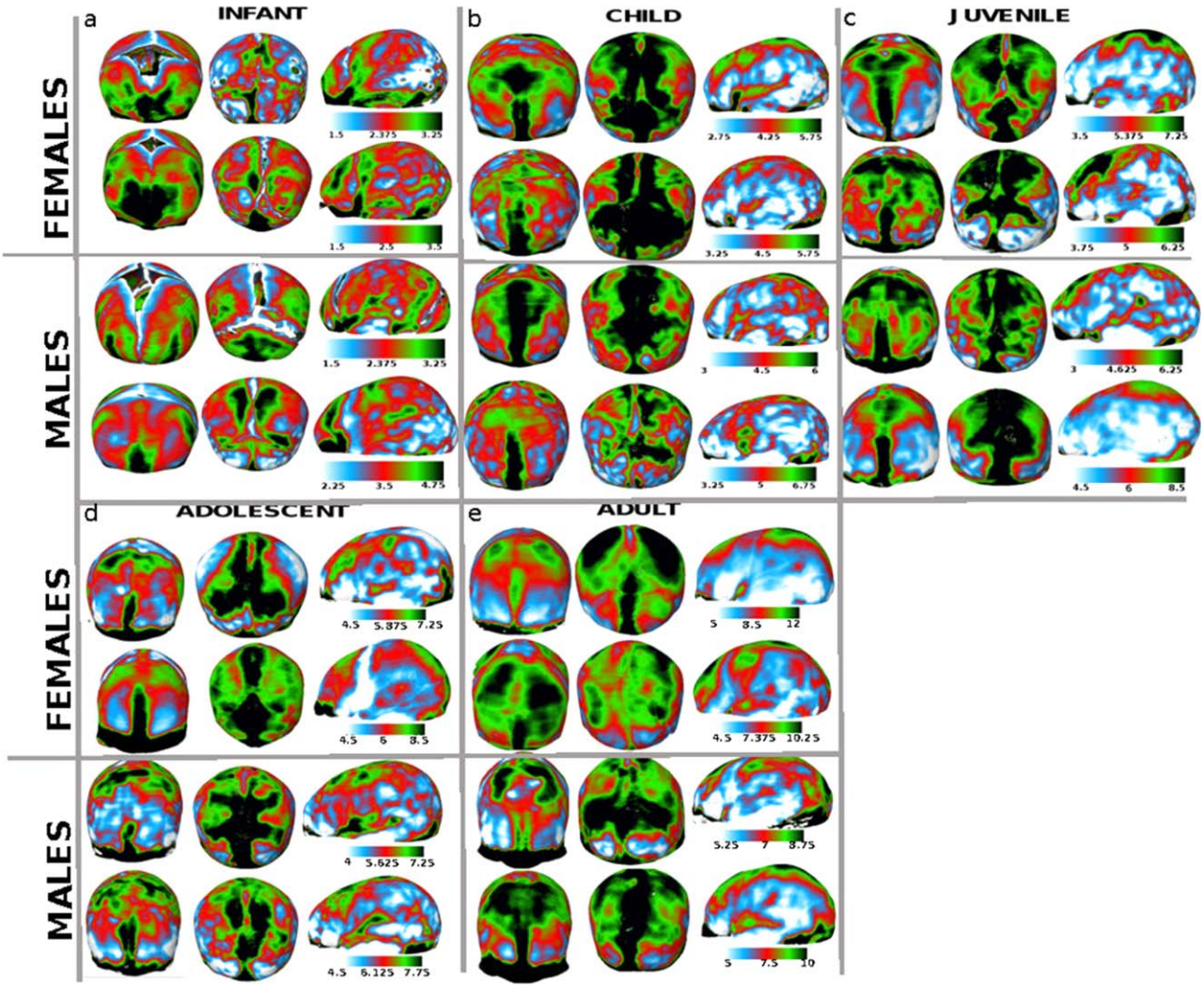

Fig. 4. Topographic mapping of CVT rendered by a particular chromatic scale for each individual, expressed in millimeters of thickness, in: (a) infants, (b) children, (c) juveniles, (d) adolescents, and (e) adults. The inferior and superior values of each particular scale limit the thickness classes with frequencies superior to 5%. Frontal view (left) shows the frontal bone and the anterior half of both parietal. Posterior view (center) shows the occipital bone and the posterior half of parietals. Lateral view (right) shows the left cranial wall.

The potential influence of brain size on CVT was already evaluated. Copes (2011) detected a very poor association between thickness and cranial capacity in adult humans. Balzeau (2013) compared adult individuals of different hominins species and observed a positive and significant correlation between CVT and EV. The present ontogenetic study suggests that CVT varies until the onset of adulthood (Table 3, Figs. 1a and 2), although EV growth is finished during childhood (Table 3, Fig. 1b). Later changes in CVT may be affected by other factors rather than brain size, such as muscular loads.

Previous works demonstrated that chewing is an important factor affecting masticatory muscle size (Copes, 2011) and human craniofacial morphology (Beecher and Corruccini, 1981; Bouvier and Hylander, 1981; Menegaz et al. 2010; Spencer and Ungar, 2000). The strains applied to the bone during contraction induce local osteoblastic responses that increase the cortical bone mass of the outer table (Biewener et al., 1986; Frost, 1986, 1987, 1988; Herring, 1993) without affecting the inner table (Moss and Young, 1960; Peterson and Dechow, 2003). Locally, the cranial vault may bear significant loads in those portions that serve as anchorage of masticatory and nuchal musculature (Behrents et al., 1978). Menegaz et al. (2010) and Copes (2011) tested experimentally the relation between craniofacial morphology and diet. Menegaz et al. (2010) reported an increase of frontal thickness in rabbits with a hard diet, and Copes (2011) detected that female mice with a soft diet had a reduction of CVT in relation to a control group.

As observed in other mammals, strains are larger over sagittal sutures than over the lateral walls of the vault and muscular contraction is dissipated along this suture (Herring and Teng, 2000). Masseter and temporal muscles exert loads on interfrontal and interparietal sutures, respectively (Behrents et al., 1978). In relation to other

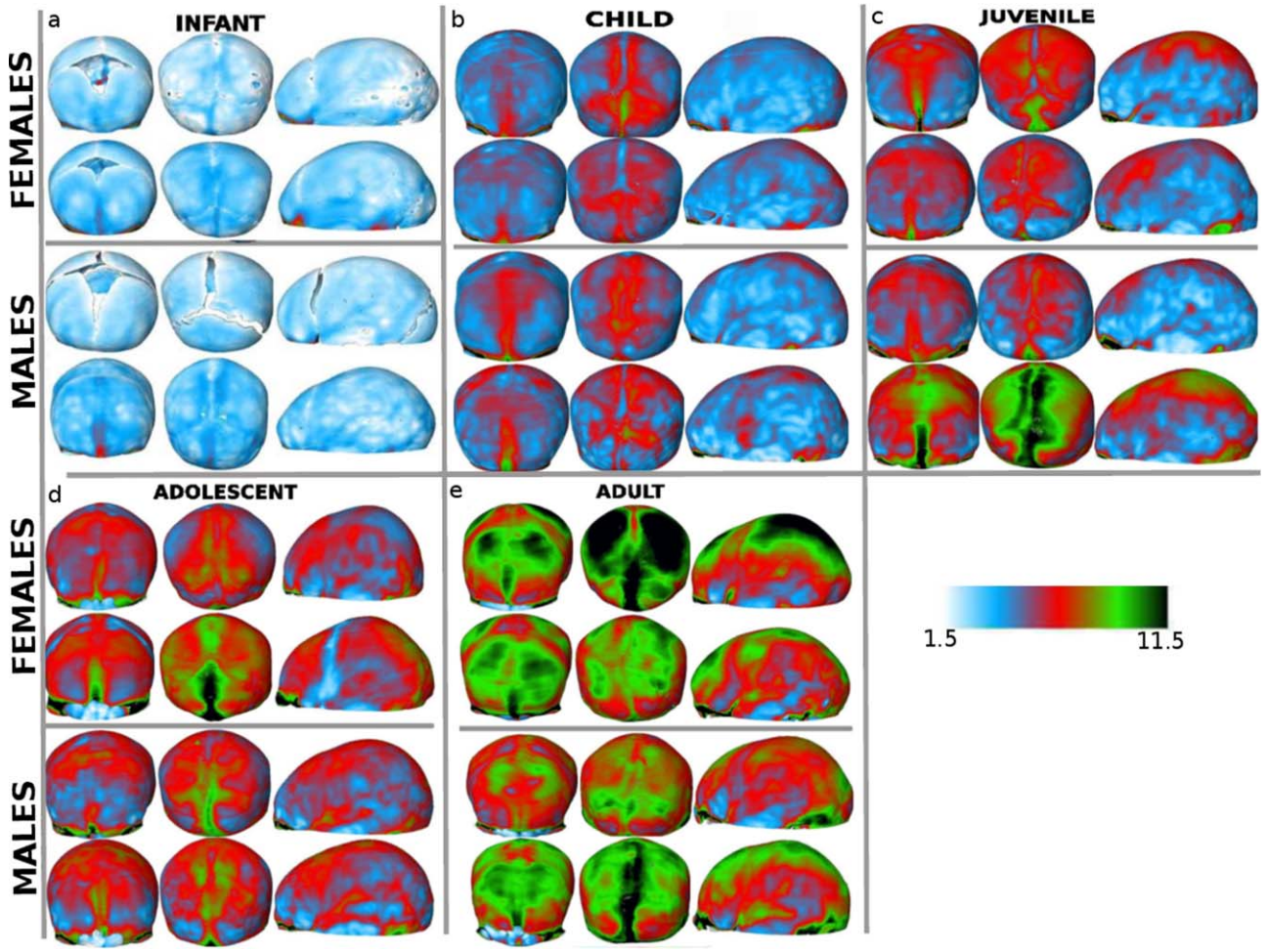

Fig. 5. Topographic mapping of CVT rendered by a common chromatic scale for all individuals, expressed in millimeters of thickness, in: (a) infants, (b) children, (c) juveniles, (d) adolescents, and (e) adults. Frontal view (left) shows the frontal bone and the anterior half of both parietal. Posterior view (center) shows the occipital bone and the posterior half of parietals. Lateral view (right) shows the left cranial wall.

mammalian species, primates have an early fusion of their vault sutures and, therefore, muscle loads are mainly transmitted along the midline. As we observed, the sagittal region is thicker than the lateral walls of the vault and these variations of thickness can be, at least in part, the result of the influence of muscular contraction on sagittal regions (Marsh, 2013).

In this study, differences between the sexes were not detected, neither in the growth trajectory of mean CVT (Table 2, Fig. 1a) nor in variation and arrangement of CVT (Figs. 2–5). Similar results were obtained by Smith et al. (1985), who did not find sexual dimorphism in human samples from the Middle East and by Balzeau (2013) in hominins. The absence of CVT dimorphism suggest that thickness may be a trait with a complex development as size differences between sexes are frequently observed in brain (Ventrice, 2011) and muscles (Raadsheer et al., 1996) that produce greater bite forces in males than females. Additional studies that assess the direct relationship between variation in CVT, brain and masticatory muscular morphology, and masticatory strain are necessary.

In sum, CVT increases during ontogeny (Table 3, Figs. 1a and 5). Similar in both sexes, an important change in CVT occurs in the period between infancy and childhood, although CVT changes are detected until later ontogeny (Table 3, Figs. 1a, 2, and 4). Thus, the first hypothesis (H1) cannot be rejected.

As previously mentioned, the most accelerated growth rates of CVT occur during the first 2 years of life, which coincides with the period of significant increase in EV (i.e., brain). However, EV and CVT trajectories are very different after childhood. Therefore, the second hypothesis (H2) cannot be completely accepted. The link between brain size and CVT is not straightforward as in infants/children the cranial vault becomes thicker with increase in cranial capacity, but under the influence of certain pathologies that increase cranial capacity (e.g., hydrocephaly) the cranial vault becomes thinner. Furthermore, along hominin evolution brain size has increased and CVT has decreased (Balzeau, 2013). This suggests that several mechanisms, not only the brain, may intervene in the development of vault thickness.

Results of this study indicate that the adult pattern of thickness arrangement is observed beginning very early in ontogeny (Fig. 4). However, differences in thickness between regions become remarkable across ontogeny,

moreover, between childhood and the juvenile period. For this reason, H3 cannot be rejected. The dynamic of bone development (i.e., formation of sutures and development of diploe), directly linked with brain protection, is probably a main factor that changes the arrangement pattern. Later in ontogeny and until adulthood, the vault bones dynamic may be changed by the influence of other functional matrices, such as muscles, brain shape (separation of hemispheres and protrusion of some lobes), and vessels that run endocranially.

In an evolutionary context, *Homo sapiens* is characterized by a low CVT (Lieberman, 1996; Nawrocki, 1991) and a particular pattern of thickness distribution and arrangement compared to other hominins (Balzeau, 2013) and other primates (Gauld, 1996). These changes are attributed to the evolution of the brain (Balzeau et al., 2012). The relevance of an ontogenetic analysis of CVT is that it provides some evidence to consider the multiple developmental factors involved in CVT variation. The adult pattern of CVT arrangement is observed from the very early moments of ontogeny and suggests that some differences between primates may be produced during prenatal life.

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