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Frontal sinus ontogeny and covariation with bone structures in a modern human population

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Abstract

In humans, the frontal sinus (FS) is located in the medial part of the supraorbital region, sometimes expanded throughout the frontal squama. It exhibits high morphological variability, but its general form appears to be constrained by surrounding structures. The goal of this study is to analyze FS growth and test for covariation between FS volume and the glabellar region, upper nasal region, bone thickness and endocranial size in a human sample from Argentina. The sample comprises 149 reconstructions derived from computed tomography images of individuals aged 0–31 years. Volume of the FS and measurements of the surrounding structures were recorded. The FS growth trajectory was assessed by parametric and nonparametric methods, and covariation was determined using correlations and partial correlations. The FS volume could be measured at an age of about 6 years and older; adults had no aplasia but hyperplasia was found in some cases. Since the most conspicuous characteristic found was variation among individuals, the nonparametric smoothing spline produced very poor fitting. The modified logistic function was the only parametric method providing significant parameters. Sexes differed in the age at which FS growth began and ended, with FS developing earlier but at a slower rate in females than in males. The FS volume did not correlate with either upper nasal width or endocranial volume, but it correlated with bone thickness measurements (mainly from the glabellar region), even when age was held constant. Expansion of the FS at the frontal poles also correlated with frontal bone thickness. Despite the difficulty in modeling and predicting the trajectory and morphology of FS, our results suggest that it is affected by its surrounding bony environment.

KEYWORDS
three-dimensional imaging, bone thickness, Glabella, morphology, pneumatization

1 | INTRODUCTION

Paranasal sinuses are air-filled spaces contained in cranial bones, that is, maxillary, sphenoid, ethmoid, and frontal, that connect with the walls and roof of the nasal cavity in many mammals. They show conspicuous characteristics such as high levels of interspecific morphological variation and a variable pattern of presence/absence across groups (e.g., Curtis, Lai, Wei, & Van Valkenburgh, 2015; Farke, 2007; Márquez, 2008; Rahmati, Ghafari, & AnjomShoa, 2016; Zollikofer & Weissmann, 2008). Their functional role is unclear (Farke, 2008, 2010; Koppe, Rae, & Swindler, 1999; Rae & Koppe, 2008). Márquez (2008) grouped all the functions ascribed to sinuses into two categories: (a) architectural or structural, such as skull lightening, brain protection or resistance to biomechanical forces; and (b) physiological, such as warming and humidification of inspired air before reaching the lungs. In addition, sinuses have been proposed to be nonfunctional (Márquez, 2008).

In mammals, the frontal sinus (FS) shows a more variable morphology and presence/absence pattern than other sinuses (Curtis & Van Valkenburgh, 2014; Farke, 2010; Rossie, 2006). For instance, in some species of Bovidae, the FS completely fills the expanded frontal bone and horncores (e.g., *Bison bison;* Farke, 2007, 2008, 2010) and in semiterrestrial and terrestrial Carnivores the FS varies in position within the frontal bone and also varies in size in relationship to general skull size and form (Curtis & Van Valkenburgh, 2014). However, both clades contain also species with complete lack of FS; it is absent in all pinnipeds and most semiaquatic carnivores sampled by Curtis et al. (2015) and in some bovids (*Procapra gutturosa*). Although FS morphology differs between species, it appears to be quite similar within species (Curtis & van Valkenburgh, 2014; Curtis et al., 2015; Farke, 2007, 2010).

In humans, the FS is contained within the frontal bone, in the medial part of the supraorbital region, sometimes also spanning through the frontal squama (e.g., Vinyard & Smith, 1997; Zollikofer, Ponce De LeÓn, Schmitz, & Stringer, 2008). It connects with the nasal cavity, borders the cranial base and the inner wall of the orbits. The pneumatization of the frontal bone begins early in postnatal ontogeny but the FS becomes visible in medical images (X-ray or CT) of individuals between about 5 and 7 years old (Fatu, Puisoru, Rotaru, & Truta, 2006; Park et al., 2010; Spaeth, Krügelstein, & Schlöndorff, 1997) and exhibits a retarded growth compared to the other sinuses (Park et al., 2010). The FS of males is larger (Selcuk et al., 2015), grows at slower rates and attains the adult size later, on average (Gagliardi, Winning, Kaidonis, Hughes, & Townsend, 2004; Prossinger, 2001) than that of females. Prossinger (2001), who studied the cross-sectional area of the FS using radiographs of children between 3 and 11 years old, predicted with a sigmoid function that FS adult size is attained at ages 23.6 and 19 in males and females, respectively, with the FS size of adult females being on average 13% smaller than that of adult males. Spaeth et al. (1997) and Fatu et al. (2006) suggested that the FS adult size is reached at earlier ages than those proposed by Prossinger (2001).

In contrast to other mammals, the human FS is remarkably variable, as demonstrated by studies comparing their respective areas (Fatu et al., 2006; Prossinger, 2001), outlines (Christensen, 2004), linear measurements (Akhlaghi, Bakhtavar, Moarefdoost, Kamali, & Rafeifar, 2016; Flanigan, Kshettry, Mullin, Jahangiri, & Recinos, 2016; Hanson & Owsley, 1980; Spaeth et al., 1997; Vinyard & Smith, 1997; Zollikofer et al., 2008) and volumes (Emirzeoglu, Sahin, Bilgic, Celebi, & Uzun, 2007; Park et al., 2010; Rae, Koppe, & Stringer, 2011). Hyperplasia of the FS has been reported in about 8–12% of adults (Fatu et al., 2006; Guerram, Le Minor, Renger, & Bierry, 2014), while aplasia (absence of pneumatization) has been found in 2–25% of humans from different geographic populations (Akhlaghi et al., 2016; Fatu et al., 2006; Flanigan et al., 2016; Hanson & Owsley, 1980; Park et al., 2010; Vinyard & Smith, 1997). Variation between populations has also been observed in FS size (Emirzeoglu et al., 2007; Hanson & Owsley, 1980; Park et al., 2010; Prossinger, 2001; Sahlstrand-Johnson, Jannert, Strömbeck, & Abul-Kasim, 2011; Vinyard & Smith, 1997).

Some evolutionary, clinical, and surgical studies have provided evidence of association between the morphology of paranasal sinuses and the surrounding bony structures (e.g., Fatu et al., 2006; Flanigan et al., 2016; Hamdy & Abdel-Wahed, 2014; Park et al., 2010; Rahmati et al., 2016; Smith et al., 2011; Štoković et al., 2016; Zollikofer & Weissmann, 2008) and between sinuses and stature in humans (Ruf & Pancherz, 1996). Studies comparing different species of mammals have shown that the FS volume is positively associated with skull size (Curtis et al., 2015; Farke, 2010; Zollikofer et al., 2008). When focusing on adjacent structures, the FS expands between the outer and inner tables of the vault (Moss & Young, 1960), in the region where the supraorbital torus develops. In line with this, previous studies have reported that the dimensions of the FS are associated with the supraorbital torus among adult humans (Vinyard & Smith, 1997) and among some other hominids and apes (Zollikofer et al., 2008). The outstanding variation of the FS and its expansion through the frontal squama suggest that the FS is a functionless structure, which expands opportunistically where bone is available and mechanically unnecessary, and contributes to reduce bone mass (e.g., Curtis et al., 2015; Farke, 2010; Weidenriech, 1924; Witmer, 1997, 1999). This process has been described as the "opportunistic epithelial pneumatization" hypothesis.

The goal of the present study is to assess ontogenetic variation and covariation of the FS in a human sample from Argentina. We assessed the growth trajectories of the FS volume in males and females. One novelty of this study is that we used different mathematical methods, much of them not previously used, in order to model FS ontogeny from infancy to adulthood. Based on literature about FS growth (Park et al., 2010; Prossinger, 2001) and sexual dimorphism (Akhlaghi et al., 2016; Emirzeoglu et al., 2007; Prossinger, 2001; Spaeth et al., 1997), males and females would reach the adult size at about 20 years old, but following different trajectories. We also assessed growth trajectories of some adjacent structures to analyze potential spatial/developmental effects. Association between traits can be inferred by comparing the ontogeny (i.e., growth trajectories) of different modules or anatomical parts or by direct test of correlation between traits (Lieberman, 2011). Based on previous studies on different paranasal sinuses, it is expected that the FS is structurally and developmentally associated with other variables, such as: (a) cranial size (Curtis et al., 2015; Zollikofer et al., 2008); (b) dimensions of adjacent structures, for example, nasal size (Butaric & Maddux, 2016; Butaric, McCarthy, & Broadfield, 2010; Holton, Yokley, & Butaric, 2013; Maddux & Butaric, 2017); and c) bone thickness and thickness of the glabellar region, as the bony environment provides the space to enable/constrain FS expansion (Curtis et al., 2015; Farke, 2010; Vinyard & Smith, 1997). The ontogenetic analysis of the FS in relation to these structures provides insight into the underlying mechanisms (e.g., the opportunistic pneumatization hypothesis) that shape the observed morphological variation among populations and species (Prossinger, 2008). In addition, results of this study may be of clinical and surgical importance as the FS morphology is associated with different pathologies (Fatu et al., 2006; Flanigan et al., 2016; Lorkiewicz-Muszyńska et al., 2015; Park et al., 2010; Prossinger, 2008). Finally, our study may contribute with useful information to human evolutionary studies, considering the phylogenetic significance of the structural relationships between the FS, the supraorbital torus, the orbits, the upper nasal cavity and the neurocranium (Athreya, 2012; Bookstein et al., 1999).

2 | MATERIALS AND METHODS

The data set consists of head computed tomography (CT) scans obtained from healthy patients at Fundación para la Lucha contra las Enfermedades Neurológicas de la Infancia (FLENI) (Buenos Aires, Argentina), which is a non-profit organization dedicated to the

TABLE 1 Cranial measurements (Figure 1)

Ab.	Name	Description
GT	Glabellar thickness (in mm)	Distance between Glabella and Foramen cecum
FST	FS thickness (in mm)	Anteroposterior thickness of FS, where GT was measured. It is an indicator of FS size at the glabellar region
BTG	Bone thickness at the Glabella	Measured as GT - FST, it is an indicator of bone thickness free from the FS contribution
FSPG	FS proportion at Glabella	Measured as FST/GT, it represents an indicator of the contribution of the FS to the glabellar or supraorbital thickness
AFT	Anterior frontal thickness (in mm)	Average of bone thickness in the right and left frontal poles of the endocranium. The frontal poles are located above the supraorbital torus
NRL	Nasal roof length (in mm)	Distance between Nasion and Foramen cecum. Since the foramen cecum is on the endocranium, this measure is just a proxy, not direct measure, of the nasal roof
UNW	Upper nasal width (in mm)	Distance between right and left Dacryons. It represents the mediolateral extension of the interorbital rims and a breadth across the nasal space (Howells, 1973), thus, a proxy of upper nasal width in humans
VT	Vault thickness (in mm)	Average of the overall vault bone thickness, already measured and analyzed in Anzelmo et al. (2015)
EV	Endocranial volume (in cm^3)	It was already measured and analyzed in Ventrice (2011) and Anzelmo et al. (2015). This measure is considered an overall size measure of the head and brain, and an indicator of potential allometric associations of the FS

prevention, diagnosis, treatment and research of neurological diseases in individuals of all ages. A cross-sectional ontogenetic sample was constructed by one of us (FV) (Ventrice, 2011), with the approval from FLENI's Ethical Committee. The sample consists of 149 individuals from 0 to 31 years old of both sexes (87 females and 62 males). Most patients of FLENI came from Buenos Aires City and adjacent urban areas, while the rest from other regions of Argentina. The Argentine population comprises genetically mixed individuals with main proportions of European and Indigenous American ancestries, according to genetic studies (Avena et al., 2012).

Individuals were scanned with a General Electric Light Speed RT16, producing for each one 275 axial CT-images with a resolution of 512 × 512 pixels and a voxel size equal to 0.449 × 0.449 × 0.625 mm. All CT-images included the neurocranium and superior facial skeleton. Each CT-image was transformed from DICOM format (Digital Imaging and Communications in Medicine format) to Analyze format for compatibility reasons; during this procedure images became anonymized with the program MIPAV (Medical Image Processing, Analysis and Visualization) (McAuliffe et al., 2001) to safeguard patient confidentiality and to use them for research purposes (Ventrice, 2011).

Cranial images were analyzed with Avizo 6.0 (Science Visualization Group). A 3D-reconstruction was obtained from CT-slices of each individual. Such reconstructions were made with a segmentation technique that uses threshold values to distinguish between different head tissues. Each threshold corresponds to the minimal intensity of a given tissue and is expressed in Hounsfield units (HU, Spoor, Jeffery, & Zonneveld, 2000). For bone segmentation, we first detected the bone minimal intensity, and then selected every pixel with a larger intensity value. The appropriate threshold value was determined empirically. The FS volume (in cm^3) was automatically calculated from the 3D reconstruction using a threshold range between −63 and 155 HU, within which only air-filled structures are segmented. We also took measurements and calculated indices for both the FS and its adjacent cranial regions (Table 1, Figure 1), which are useful indicators of morphological associations. Specimen information and raw measurement data can be obtained from http://naturalis.fcnym.unlp.edu.ar/repositorio/_documentos/sipcyt/database.csv

We evaluated the FS growth trajectory by different methods because its extreme variability leaded to statistically "noisy" data (Prossinger, 2008). On the one hand, we used a nonparametric smoothing spline to describe trajectories according to sex and chronological age. We explored different values of the smoothing parameter λ -from 0.1 to 100- to determine the best bias-variance trade-off along the trajectory. Non-parametric methods are sometimes preferable to the parametric methods for describing growth because curves are estimated without the need to fit any particular shape; however, they have the disadvantage of providing neither significance tests nor parameter estimates. However, we applied parametric methods. Most anatomical structures follow an asymptotic growth trajectory; hence, data from both sexes were fitted to different nonlinear models to find the best-fit model. We used growth functions commonly used in the literature, namely the logistic, Weibull, Gompertz, and monomolecular functions (Koppe, Klauke, Lee, & Schumacher, 2000; Koya & Goshu, 2013; Topal & Bolukbasi, 2008) and a modified logistic equation (Prossinger, 2001, 2008). Models were calculated with InfoStat software. The best-fitting model was the modified logistic function, with the following equation:

$$V = \frac{\alpha}{1+\beta * e^{-\gamma * x}}$$

where V is the FS volume, x is the age and α, β, and γ are parameters; α is the estimated adult size, β represents the age at which maximum growth is reached, and γ is a function of growth rate. Additionally, outlines of FS were also provided to depict variation in morphology and distribution of the FS within the frontal bone.

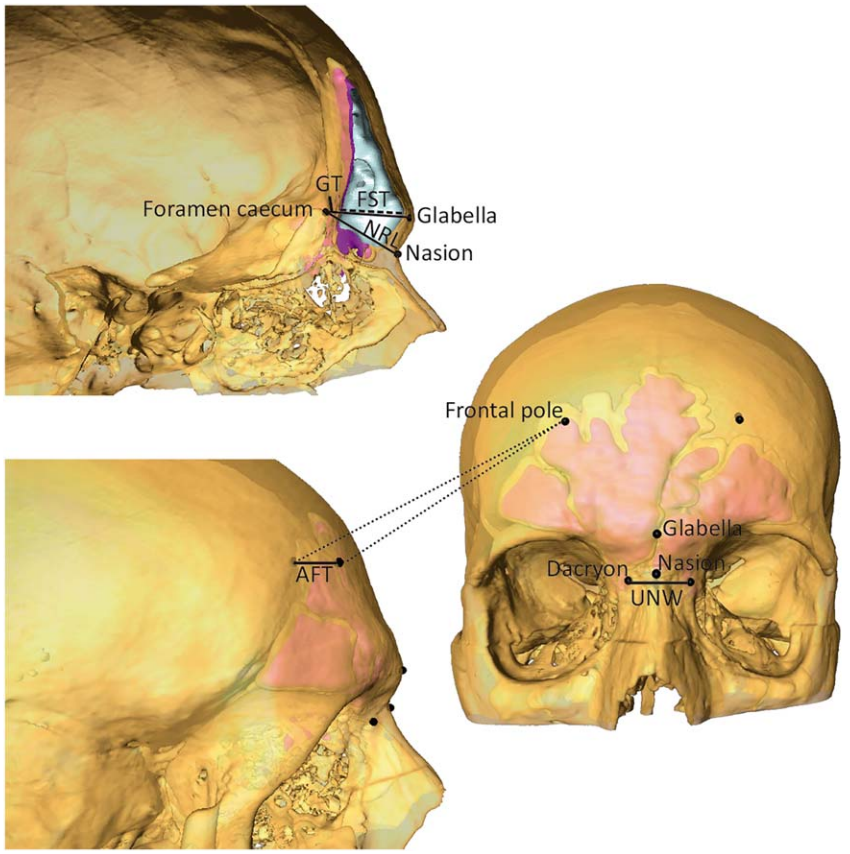

FIGURE 1 Measurements of variables directly calculated on CT images. For definitions of variables see Table 1

We also analyzed the growth trajectories for each variable to test for associations between the FS and cranial structure. The Kolmogorov–Smirnov test indicated that the FS volume was not normally distributed and hence raw data were cubic-root transformed to meet normality and homoscedasticity assumptions. Correlations and partial correlations were performed to examine associations between FS and the studied cranial variables. Finally, we divided the adult sample into two groups, depending if the FS is present or absent at the frontal poles and we used a Student's one-tailed *t*-test to check for significant differences between both groups. These statistical analyses were carried out with InfoStat software.

3 | RESULTS

In the studied sample, the FS could be visualized, segmented and subsequently measured in children from 6 years, but also in one individual of 4 years old. The FS volume could not be calculated in 21 subadult individuals, suggesting delayed FS development or aplasia. All individuals older than 11 years old presented FS; five adult males showed hyperplasia.

Growth trajectory of the FS was generated from a cross-sectional sample of 128 individuals. This was described using a smoothing spline and different values of the smoothing parameter λ were explored to find out the best one (Table 2). The growth trajectories in both sexes were described with λ values of 10 or 100, but yielding poor fitting, especially for females. Improved fitting was achieved using lower λ values, but no trajectory could be found, even after removal of hyperplasic individuals.

The FS grows rapidly until middle adolescence, and no clear variation pattern is observed thereafter. Females are likely to attain the adult FS size earlier than males (at approximately 15 and 20 years old, respectively; Figure 2). In addition, the FS volume also varies greatly among individuals after middle adolescence, with some adults having lower values compared to most subadults (Figure 2).

Trajectories were then explored with parametric methods. The limitation of these methods was that adults with hyperplasic FS (see below) had to be removed for equation modeling, as a significant asymptote (size at adulthood) could not be obtained otherwise.

All equations provided solutions with low mean square error, but we selected the modified logistic function (Prossinger, 2001) because it

TABLE 2 Adjustment (r^2) of smoothing splines with different λ values

λ	Females	Males (all individuals)	Males (removing hyperplasic individuals)
0.1	0.529	0.687	0.753
1	0.372	0.572	0.645
10	0.257	0.488	0.572
100	0.169	0.438	0.539

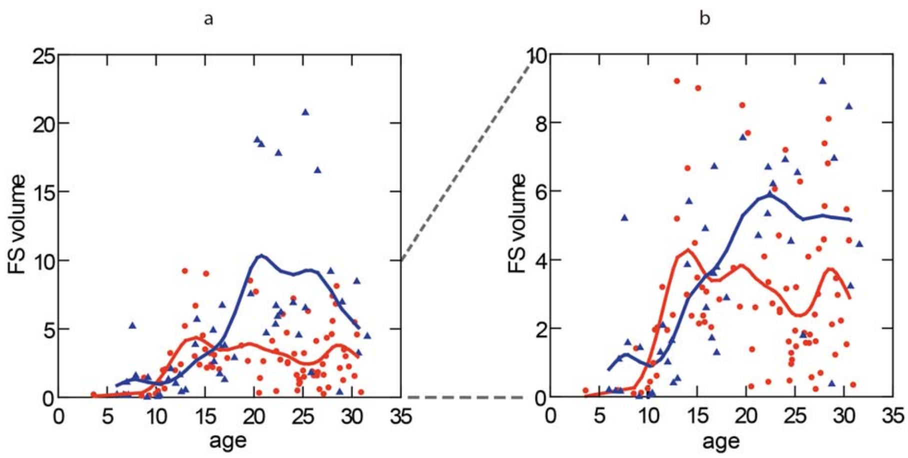

FIGURE 2 FS volume of males (blue triangles) and females (red circles) versus age (a) including the entire sample; (b) excluding hyperplasic individuals. Smoothing splines with $\lambda = 10$ in both cases

fitted our data better than the other models (Table 3). In both sexes, probabilities associated with the parameters α, β, and γ were below 0.001 (Table 3).

The FS may start growing earlier in females than in males; FS maximum growth rate is attained at 8.95 and 12.27 years old in females and males, respectively (Table 4). When analyzing growth rate functions (Figure 3), we notice that the FS grows at higher rates in males (0.93 cm^3/year) than in females (0.78 cm^3/year) and attains adult size later in males than in females (Table 4; Figure 3). Differences in FS growth rate and in the age at which sexes reach adult FS size (14.6 years old for females and 20.0 years old for males) may explain FS dimorphism in adults (Figures 2 and 3).

The variation in ectocranial outlines of FS were depicted in a subsample of subadults and adults (Figure 4). Based on shape outlines, the FS initiates as a small vesicle and expands upward, extending alongside the frontal squama in a fan- like manner.

The adult group was delimited from subadults according to the age at which individuals attained 99% of the adult FS size (age > 20.0 in males and > 14.6 in females) (Table 4). Both adult and subadult groups showed a remarkable variation in FS volume (Table 5); in subadults it was possibly due to the inclusion of data from individuals undergoing a growing phase.

Ontogenetic trajectories of all the analyzed variables are depicted in Figure 5. Three types of trajectories can be observed: (a) the endocranial volume attains most of its adult size very early in ontogeny; (b) glabellar thickness, anterior frontal thickness, nasal roof length, and vault thickness follow somewhat constrained trajectories, but they exhibit delayed development with respect to the endocranial volume; and (c) absence of any clear pattern of change during postnatal ontogeny, as is the case for the remaining traits (Figure 5). The growth trajectory of FS size would be included in the latter type. If developmental mechanisms provide key insights to understand the evolution of complex features, we observed different patterns of ontogenetic variation in most of the variables analyzed here.

Results of correlations and partial correlations are presented in Table 6. All correlations between FS volume cubic root and the studied

TABLE 3 Models applied and parameters obtained in the estimation of FS ontogeny in males (M) and females (F)

Model	Sex	CMError	No of parameters	Signification of parameters
Logistic	F	4.86	3	2 param.***; 1 nonsignificant
	M	3.75		1 param***; 1*; 1 nonsignificant
Weibull	F	9.36	2	2 param. nonsignificant
	M	14.54		1 param.*; 1 nonsignificant
Gompertz	F	4.87	3	1 param.***; 2 nonsignificant
	M	3.77		1 param***; 1*; 1 nonsignificant
Monomolecular	F	5.25	3	1 param.***; 2 nonsignificant
	M	3.95		1 param.**; 1*; 1 nonsignificant
Adapted logistic model	F	4.71	3	3 param.***
	M	3.92		3 param.***

[a]*$p < .05$. **$p < .01$. ***$p < .001$.

TABLE 4 Results obtained with the modified logistic function

	Females	Males
Age of beginning of growth	6	8
Maximum growth rate	0.78 cm^3/year	0.93 cm^3/year
Age of maximum growth	8.95	12.27
Adult volume	3.29 cm^3	5.36 cm^3
Age of attainment of 95% adult size	12.6	17.3
Age of attainment of 99% adult size	14.6	20.0

variables were positive except for bone thickness at the glabellar region, which decreased as FS increased (Table 6a), implying that individuals with higher degree of frontal sinus pneumatization have a thinner frontal bone in the glabellar region. FS volume correlates neither with upper nasal width nor with endocranial volume.

Since measurements made on growing structures may confound results, we calculated partial correlations at constant age. Results were very similar to those obtained in Table 6a (Table 6b), albeit with reductions in the correlations of upper nasal width and endocranial volume with all other variables. Overall, it seems that bone thickness is more linked to the expansion of the FS rather than to upper nasal or endocranial dimensions. Partial correlations were thus calculated, holding constant age and mean vault thickness. Results were similar to those in Table 6b, with the exception of the partial correlations between anterior frontal thickness with all other variables, which became non-significant due to its association with vault thickness (Table 6c).

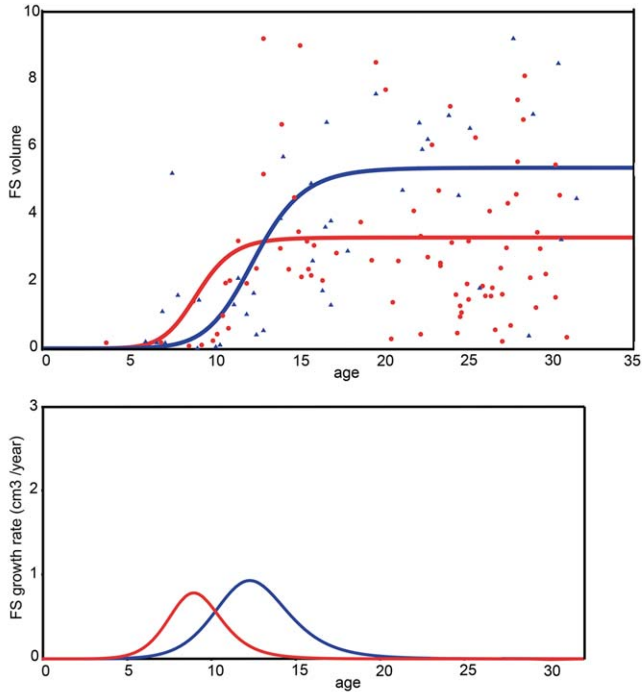

FIGURE 3 FS growth modeled with the modified logistic function: (a) growth trajectory of FS volume for males (blue triangles) and females (red circles), in cm^3; (b) FS growth rate, in cm^3/year

The FS is extended through the frontal poles in 44.5% of the individuals who reached the adult FS size. We compared cranial variables between adults with FS present and absent at the frontal poles using a one-tailed *t* test. To this aim, we first performed a *z*-standardization of data for each sex separately because most of adults were females, and then we pooled data from both sexes. The group with FS extension at the frontal poles showed significantly higher means for the studied variables than the group without it, except for glabellar bone thickness (Table 7). Differences between groups in bone thickness at the frontal poles and FS volume were particularly significant ($p < .01$).

4 | DISCUSSION

In this study, we modeled the FS growth with parametric and nonparametric methods. The modified logistic function developed by Prossinger (2001) was the model that best fitted the data, but only after the hyperplasic individuals were removed. Prossinger (2001) predicted that adult size of the cross-sectional area is reached at 23.6 and 19 years old in males and females, respectively, based on a sample between 3 to 11 years old children. We found in the Argentine sample that 99% of adult FS volume was reached at younger ages than those of Prossinger (2001), 20.0 and 14.6 years old, in males and females, respectively (Table 4). In agreement with our results and those of Prossinger (2001), Park et al. (2010) observed in individuals of Asian ancestry an earlier FS growth for females than for males. In contrast to previous studies (Prossinger, 2001), our results indicate that growth rates are higher in males than in females. Nevertheless, parametric and non-parametric adjustments cannot adequately explain the remarkable variation observed among adults.

Frontal sinus outlines (Figure 4) are similar in males and females, but highly variable among individuals and even between the right and left FS lobes of a same individual, as already observed by other authors (e.g., Christensen, 2004). This outstanding interindividual variability led to some authors (Akhlaghi et al., 2016; Tucunduva, Ferreira, Baladi, & Freitas, 2011) to propose that the FS morphology is a potentially useful tool for forensic identification.

High levels of variation in the FS-size were reported by Fatu et al. (2006) in adults between 20 and 45 years old. Furthermore, Fatu et al. (2006) found an enlargement of the sinusal cavity in individuals older than 60 years old, whereas other authors observed a significant reduction in FS dimensions with age during adulthood (Akhlaghi et al., 2016; Emirzeoglu et al., 2007). The cross-sectional approach of this study does not allow us to determine whether or not FS size remains constant during adulthood, but since cranial structures changes with aging, some cranial dimensions are reduced (Fuchs, Cocilovo, & Varela, 2015; Kloss & Gassner, 2006; Sardi, Anzelmo, Barbeito-Andrés, & Pucciarelli, 2011), while vault thickness seems to increase (Adeloye, Kattan, & Silverman, 1975; Israel, 1973)-, it may influence the dynamic behavior of the FS.

The variation in FS size found among the adults of the studied sample from Argentina is partly due to the FS hyperplasia present in

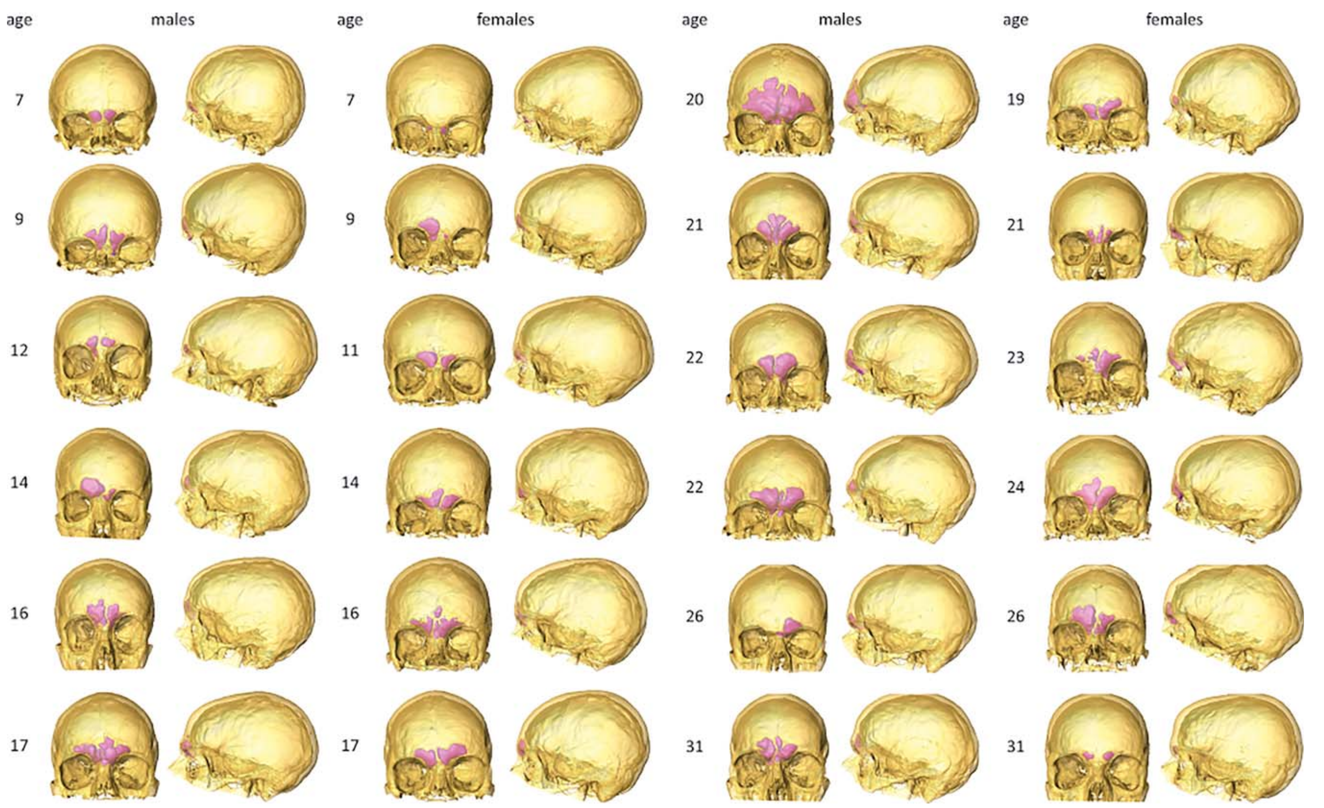

FIGURE 4 Morphology and distribution of the FS through the frontal bone in subadults and adults

five males (6% of adult individuals). This trait is relatively frequent in human populations; probably caused by increased osteolytic activity during bone resorption; as a result, the sinus extends antero-posteriorly either toward the outer diploë of frontal bone, toward the inner plate, or toward lateral structures (Fatu et al., 2006). It has been found in 2–10% of humans from different geographic populations (Akhlaghi et al., 2016; Fatu et al., 2006; Flanigan et al., 2016; Guerram et al., 2014; Park et al., 2010), in 23.7% of Melanesians (Vinyard & Smith, 1997) and in more than 25% of Inuits (Hanson & Owsley, 1980). In disagreement with other studies reporting a high frequency of FS aplasia in different populations (Akhlaghi et al., 2016; Fatu et al., 2006; Flanigan et al., 2016; Hanson & Owsley, 1980; Park et al., 2010; Vinyard & Smith, 1997), it was not found in our sample.

The FS size differs between human populations. We obtained average adult volumes of 8.67 and 3.14 cm^3 for males and females, respectively (Table 5). Mean FS volume was reported to be 3.50 cm^3 in samples from Asia (Park et al., 2010) and 11.6 cm^3 from Turkey (Emirzeoglu et al., 2007). In regard to the mean FS area, males and females from Austria showed values of 12.05 cm^2 and 10.5 cm^2, respectively (Prossinger, 2001); it was 0.77 and 1.07 cm^2 for males and 1.47 and 0.67 cm^2 for females of two Inuit samples from the Hudson Bay (Hanson & Owsley, 1980); while Melanesian aborigines had a mean FS area of 4.68 cm^2 (Vinyard & Smith, 1997). Despite variation between populations, differences in FS volume and area may also be accounted for by the measuring methods. In addition, environmental variables have been suggested to predict sinus size between populations. Selcuk et al. (2015) found that people born and living in a cold and dry climate at high altitude had a mean FS volume of 5.51 cm^3, while it was 3.76 cm^3 for people born and living on the coast at sea level in a temperate climate in Turkey. In contrast, Koertvelyessy (1972) and Shea (1977), who analyzed the relationship between the FS and cold climatic conditions, reported smaller FS for Inuit populations. In a study involving a different Inuit population, Hanson and Owsley (1980) obtained frequencies of bilateral absence ranging between 25.3 and 48.4%. However, some specimens of Neanderthals tend to exhibit conspicuous FS occupying most of the supraorbital torus despite the fact that they are thought to have been cold-adapted (Bookstein et al., 1999; Zollikofer et al., 2008).

TABLE 5 Descriptive statistics of FS volume

	n	*X* ± *SD*	CV (%)
Subadult males (under age 20)	27	2.27 ± 2.17	95
Subadult females (under age 14.6)	18	2.20 ± 2.52	115
Adult males	20	8.67 ± 6.17	71
Adult females	63	3.14 ± 2.19	69

Because the morphology and association of the components of anatomical systems are affected by developmental and functional factors, we expected that traits sharing spatial, functional or developmental attributes are linked and vary in a coordinated manner (Olson & Miller, 1958). The extent of the maxillary sinus, which is the most

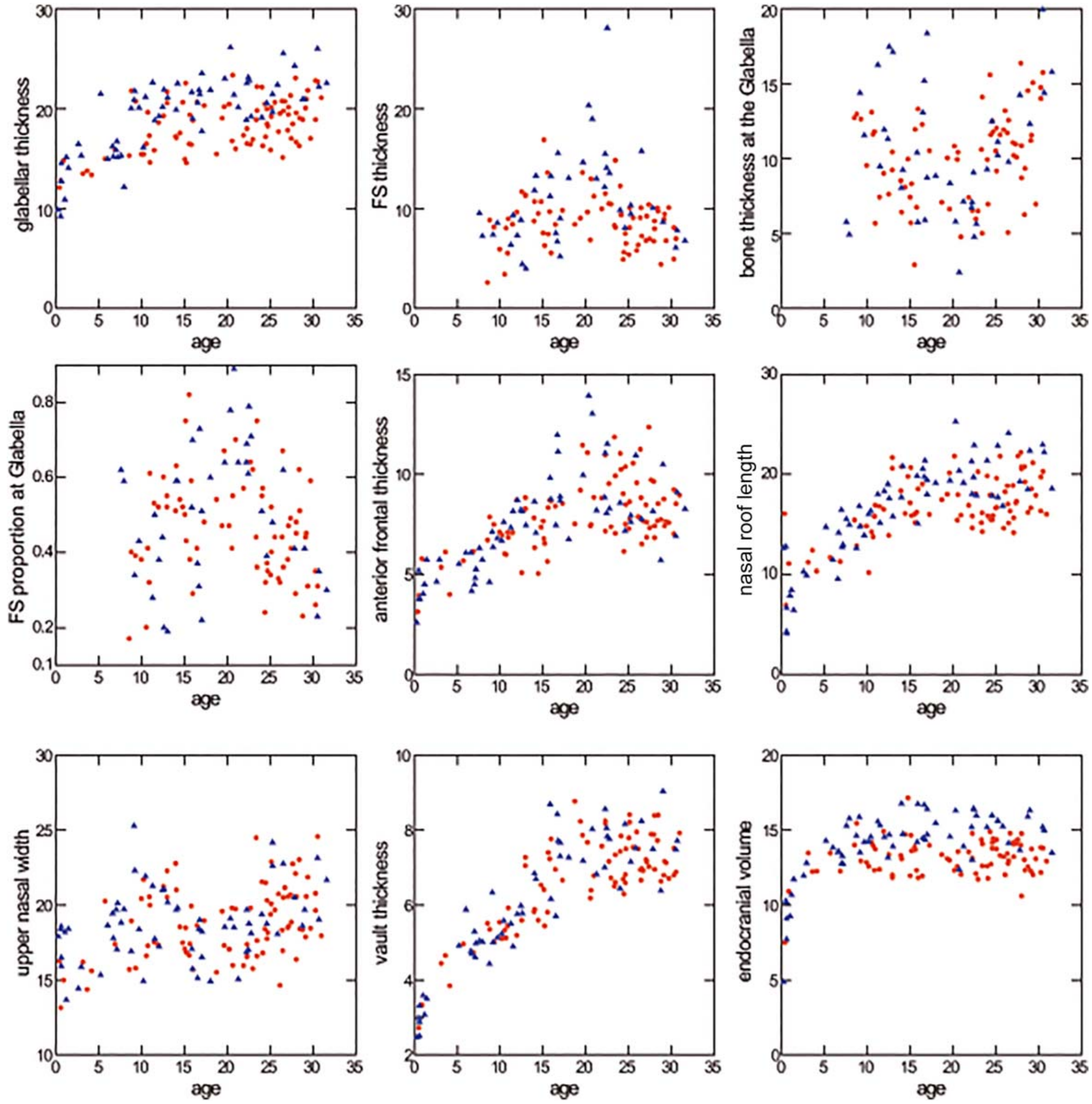

FIGURE 5 Ontogenetic variation in cranial variables for males (blue triangles) and females (red circles). For definitions of variables see Table 1

studied of the paranasal sinuses, is known to be influenced in New World monkeys by the relative dental size and the growth of adjacent skeletal structures of the maxilla; histomorphometric studies have confirmed that the growing maxillary sinus extends into areas without constraints (Smith et al., 2010, 2011). In humans, the maxillary sinus is larger in individuals with larger faces and it accommodates in the available space left by the lateral nasal walls: individuals with narrower nasal cavities present larger maxillary sinuses (Butaric & Maddux, 2016; Butaric et al., 2010; Holton et al., 2013). However, a recent study of Maddux and Butaric (2017), which compares samples of different geographic origins, shows that the maxillary sinus extends more laterally and more inferiorly in individuals with taller zygomaticomaxillary interfaces (e.g., taller midfacial skeletons) compared to individuals with shorter midfaces.

Similar results would be expected for the FS, which develops in a region that involves the endocranium, the nasal cavity, the orbits and surrounding bony structures, such as the supraorbital torus. Results indicated that all the analyzed variables show very different growth trajectories (Figure 5), being some structures highly canalized, whereas others present stochastic patterns of growth. This study did not include facial dimensions, which are expected to be associated with FS size (Zollikofer et al., 2008); however, the latter was associated neither with upper nasal width nor with endocranial volume, suggesting that variation in FS size in the Argentine sample would not be explained solely by allometry. This result contrasts with those obtained in other studies, for example, FS size and shape were correlated with cranial size and shape in other mammals (Curtis et al., 2015; Farke, 2010); and FS dimensions were positively correlated with interorbital space width in adult hominids, humans and great apes (Zollikofer et al., 2008).

Measurements of structures in the direct environment of the FS are, in contrast, positively correlated with FS size (Table 6). The

TABLE 6 Pearson correlation matrix

(a) Simple correlations									
	FS volume	GT	FST	BTG	FSPG	AFT	NRL	UNW	VT
GT	0.422**								
FST	0.667**	0.328**							
BTG	−0.319**	0.459**	−0.658**						
FSPG	0.534**	−0.090	0.863**	−0.917**					
AFT	0.466**	0.586**	0.415**	−0.127	0.263**				
NRL	0.720**	0.679**	0.396**	0.040	0.181	0.629**			
UNW	0.126	0.334**	−0.086	0.261**	−0.174	0.234**	0.349**		
VT	0.540**	0.630**	0.255**	−0.021	0.144	0.760**	0.755**	0.277**	
EV	0.142	0.572**	0.204*	0.040	0.069	0.425**	0.484**	0.232**	0.497**
(b) Partial correlations (age = constant)									
	FS volume	GT	FST	BTG	FSPG	AFT	NRL	UNW	VT
GT	0.342**								
FST	0.698**	0.291**							
BTG	−0.392**	0.472**	−0.673**						
FSPG	0.589**	−0.111	0.864**	−0.920**					
AFT	0.324**	0.223*	0.363**	−0.156	0.257*				
NRL	0.650**	0.464**	0.340**	0.025	0.172	0.223*			
UNW	0.111	0.159	−0.103	0.220*	−0.158	−0.060	0.091		
VT	0.445**	0.186	0.328**	−0.177	0.260*	0.478**	0.387**	−0.114	
EV	0.174	0.258*	0.162	0.077	0.031	0.027	0.142	−0.004	0.113
(c) Partial correlations (age and vault thickness = constant)									
	FS volume	GT	FST	BTG	FSPG	AFT	NRL	UNW	
GT	0.295**								
FST	0.652**	0.248*							
BTG	−0.355**	0.522**	−0.691**						
FSPG	0.547**	−0.168	0.854**	−0.920**					
AFT	0.141	0.155	0.249*	−0.083	0.156				
NRL	0.578**	0.432**	0.268**	0.103	0.085	0.047			
UNW	0.182	0.185	−0.070	0.205*	−0.134	−0.006	0.148		
EV	0.139	0.243*	0.133	0.099	0.001	−0.032	0.107	0.010	

[a] *$p < .05$. **$p < .01$

expansion of the FS at the poles is correlated with frontal bone thickness and FS volume correlates with many measurements at the glabellar region (Table 7). Furthermore, bone thickness at the glabellar region is reduced in individuals with greater FS thickness at the Glabella. This means that FS size keeps some allometric relationship with bone size and that bone is removed for sinus expansion.

In a Melanesian adult sample, Vinyard and Smith (1997) also found significant correlations between the FS area and the dimensions of the medial supraorbital torus, but not between the FS area and the dimensions of the lateral supraorbital torus. Nevertheless, glabellar dimensions and other robust traits are known to correlate with cranial size (Lahr & Wright, 1996; Nowaczewska, Kuźmiński, & Biecek, 2015; Vinyard & Smith, 2001) and the antero-posterior projection (Athreya, 2012), suggesting that the influence of some facial measurements on FS dimensions should not be ruled out. Furthermore, the small FS in Inuits observed by Koertvelyessy (1972) and Shea (1977) may be associated with the low levels of cranial robusticity reported by Lahr and Wright (1996) and Baab, Freidline, Wang, and Hanson, (2010).

TABLE 7 *T*-test between individuals with FS extended and absent at the frontal poles

	FS present		FS absent		
	n	Average	*n*	average	*T*
FS volume	33	0.50	41	−0.41	4.37**
GT	33	0.09	41	−0.07	0.69
FST	32	0.26	34	−0.24	2.12*
BTG	32	−0.15	34	0.14	−1.16
FSPG	32	0.25	34	−0.23	2.03*
AFT	33	0.41	40	−0.31	3.27**
NRL	33	0.24	41	−0.19	1.87*
UNW	33	0.16	41	−0.13	1.25
VT	31	−0.01	39	0.01	−0.10
EV	33	−0.26	41	0.21	−2.05

[a]* $p < .05$. ** $p < .01$.

5 | CONCLUSION

The importance of an ontogenetic study is that it enables to assess the frontal bone pneumatization patterns and the potential influence of adjacent structures in FS growth, size, and distribution. A longitudinal sample would be a better approach to highlight developmental mechanisms; however, the risk of irradiation makes not possible such an approach at the present time.

Our results obtained with a cross-sectional human sample from Argentina coincide with those obtained in other studies. We found a highly variable pattern of frontal bone pneumatization during ontogeny. As was expected, the FS growth trajectories of males and females differed in growth rates and in the age at which adult FS size was attained. However, the huge degree of variation in adult FS size prevented us from developing a model that can describe the trajectory of FS growth.

Contrary to what was expected, the FS volume correlated neither with cranial size nor with upper nasal width. However, it tended to be significantly larger and more expanded in individuals with thicker frontal bones and therefore with thicker Glabella. The fact that FS correlated with bone thickness measurements (in particular glabellar thickness) supports the "opportunistic pneumatization" hypothesis. The thickening of the frontal bone begins early in ontogeny as the diploë develops and it increases until adulthood (Anzelmo, Ventrice, Barbeito-Andrés, Pucciarelli, & Sardi, 2015), thus providing the environment for FS expansion, which would be only constrained by the inner and outer tables of the frontal bone. Further studies comparing human populations with different levels of glabellar and supraorbital projections and frontal bone thickness will enable to get greater insights into morphological associations of human FS variation.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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