Early and Middle Pleistocene hominins from Atapuerca (Spain) show differences in dental developmental patterns

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Abstract

The Bayesian statistical approach considers teeth as forming a developmental module, as opposed to a tooth-by-tooth analysis. This approach has been employed to analyze Upper Pleistocene hominins, including Neandertals and some anatomically modern humans, but never earlier populations. Here we show its application on five hominins from the TD6.2 level of the Gran Dolina site (*Homo antecessor*, Early Pleistocene) and the Sima de los Huesos site (Middle Pleistocene) of the Sierra de Atapuerca (Burgos, northern Spain). Our results show an advanced development of the third molars in both populations with respect to modern *Homo sapiens*. In addition the Sima de los Huesos hominins differ from *H. sapiens* and *H. antecessor* in the relatively advanced development of their second molar. The relative mineralization of I1/M1 in both of these hominin populations is similar to that of modern humans, as opposed to that of Neandertals, which appear to be unique. These observations, combined with reduced enamel formation times, appear to indicate a shorter ontogenetic period in the hominins from Gran Dolina and Sima de los Huesos in comparison to modern humans.

Introduction

Dental development studies on hominins typically focus on enamel and dentine time formation, and/or the sequence of dental maturation (Beynon and Dean, 1988; Tompkins, 1996a; Dean et al., 2001; Guatelli-Steinberg et al., 2018).

Studies of enamel and dentine time formation rely on the fact that tooth crowns and roots form through rhythmic cellular secretion producing a permanent record of mineralized growth layers in enamel and dentine (Smith, 2008). Dental age assessment based on counts of these incremental characteristics in enamel and dentine is an accurate, species-specific method and so independent of modern human or ape dental patterns (Bromage and Dean, 1985; Smith, 2008). Thus, the application of this kind of approaches allows us to assess ontogenetic variation between fossil and living taxa. However, these studies show some limitations. There are two types of layers in enamel and dentine: short-(daily) and long-period (> daily) increments. While long-period lines on tooth crowns (perikymata) and roots (periradicular bands) can be counted on the tooth surface, the count of short-period lines should be performed on histological sections (Smith, 2008). Since histological methods are destructive it is not possible to apply them in much of unique fossil material. Because of this, in main of fossil specimens the crown and root formation is estimated which can contribute to some controversial results (Ramirez Rozzi and Bermúdez de Castro, 2004; Guatelli-Steinberg et al., 2007; Guatelli-Steinberg, 2009). Moreover, even in those cases in which we can obtain an accurate estimation of crown and root formation, it is important to note that timing is only a part of the pattern of dental development. For instance, the same tooth can show the same timing in the same tooth of two different individuals, but in different sequence to the other teeth (Braga and Heuze, 2007). Thus, the use of histological methods along to those assessing the sequence of dental maturity is indispensable in order to obtain a complete picture of dental development process.

Traditionally, the study of variation in the sequence of dental maturation has been addressed only between pairs of teeth (Tompkins, 1996b; a) or taking into account the ages (Smith, 1986). However, these approaches have several methodological shortcomings. First, they do not consider that teeth are functionally, developmentally and topographically associated with each other. Second, the sequence of dental maturation seems to be more robust than the age of stage appearance. Thus, the study of variation in the sequence of dental maturation should be independent of chronological age.

One way to overcome these methodological shortcomings is to adopt a probabilistic approach using all teeth. In this sense, an analytical approach using Bayesian statistics to quantify variability in sequences of key events during tooth mineralization, independent of chronological age, was proposed (Braga and Heuze, 2007). This method considers the tooth within the mineralization sequence as a series of dependent units, growing within a developmental and hierarchical module. A statistical probability is determined for the likelihood of a particular dental mineralization sequence (DMS) to be present within known modern human variation. This modular system presents some properties (Raff, 1996): 1) dental development presents an autonomous, genetically discrete organization, 2) it is formed by hierarchical units, 3) it has a physical place within the developing system, 4) the degree of connectivity between modules presents different levels, and 5) it displays temporal transformations. Overall, the variability in the patterns or DMSs is relevant in human evolution, as these processes allow to assess possible foundation for morphological changes (Braga and Heuze, 2007).

This approach has been recently applied to Neandertals (Bayle et al., 2009a; Quam et al., 2015), to an Upper Paleolithic specimen from La Madeleine (Bayle et al., 2009b), and to the Lagar Velho individual (Bayle et al., 2010), a potential hybrid specimen between Neandertals and modern humans (Duarte et al., 1999). Remarkably, both Neandertals and the Lagar Velho specimen showed a DMS that is not known to exist in modern human variation, whereas the La Madeleine individual presented a DMS that falls within the known variation of modern *H. sapiens*. Moreover, the pattern of dental development of the Lagar Velho specimen is only present within the Neandertal variation. Overall, Neandertals show a proportionally advanced stage of mineralization of the first molar in comparison to their proportionally delayed stages of mineralization of the incisors. Interestingly, this statistical approach has been applied to hominins older than Neandertals in this study. Therefore, the Atapuerca hominins may give some clues on the changes of the pattern of dental development on earlier stages of human evolution.

The only two archaeological sites from Atapuerca included in this study are Gran Dolina and Sima de los Huesos. Level TD6.2 of the Gran Dolina site (~0.9-0.8 Ma) contains more than 160 human fossil remains representing at least 8 individuals attributed to the species *Homo antecessor* (Moreno et al., 2015; Bermúdez de Castro et al., 2017; Bermúdez-de-Castro et al., 2017; Duval et al., 2018). The second site is Sima de los Huesos (SH) (~0.43 Ma), which contains more than 7000 human fossil remains attributed to at least 28 individuals whose taxonomical attribution is still under discussion, although genetic and morphological data strongly suggest that these hominins belong to the Neandertal clade (Arsuaga et al., 2014).

Previous studies attempted to evaluate the patterns of dental maturation from these two fossil populations by treating tooth types as independent units. The information provided by the study of three hominins from the Gran Dolina site (Bermúdez de Castro et al., 1999, 2010) indicated relatively advanced calcification in the M3. However, hominin XVIII from the Sima de los Huesos site (Fig. 1) displayed a relatively delayed development of the lower and upper canines, a more advanced development of the lower second molars, and notably advanced development in the upper and lower third molars (Bermúdez de Castro and Rosas, 2001). Only some teeth of the lower dentition of hominin XVIII were studied under the Bayesian frame, showing that there were not differences in regard to modern humans (Bayle, 2008).

Here, we present a Bayesian analysis of the relative dental development of five hominins from two Early and Middle Pleistocene European populations uncovered in two archaeopaleontological sites from the Sierra de Atapuerca (Burgos, Spain). The Bayesian approach is applied to the pattern of dental development of two hominins from the Sima de los Huesos site (XVIII and XXV) and three hominins of *H. antecessor* from the Gran Dolina-TD6.2 site (H1, H3, H11), which treats teeth as interdependent units. This study complements the one published recently on the methods of analyzing the absolute timing and pattern of lateral enamel formation (Modesto-Mata et al., 2020).

Materials and Methods

Materials

The specimens analysed in this paper include two hominins from Sima de los Huesos-SH (XVIII and XXV) and three specimens of *H. antecessor* (H1, H3 and H11) from Gran Dolina-TD6.2 (Supplementary Table 1 and Supplementary Table 2, respectively).

The complete permanent dentition (32 teeth) and the four deciduous second molars are present in hominin XVIII (Fig. 1). The hominin XXV has complete permanent lower dentition (18 teeth) and two deciduous second molars (Supplementary Fig. 1). The dentitions of the hominins from Gran Dolina are not complete. H1 is composed of 16 teeth (Supplementary Fig. 2), whereas H3 is composed of 9 upper teeth (Supplementary Fig. 3) .

The developmental stages of the permanent dentition of fossil were scored using the system developed by Demirjian et al. (Demirjian et al., 1973), while deciduous dentition was scored based on the system established by Liversidge and Molleson (Liversidge and Molleson, 2004). The teeth and mineralisation stages of the TD6.2 hominins and the SH specimens are in Table 1. Tooth mineralisation stages of fossil hominins were identified independently by three co-authors (RG-G, YQ, MM-M). Discrepancies appeared in less than 4% of the teeth, and they were present over the latest stages of development of the root.

When establishing the mineralization stages of the TD6.2 hominin H11, which corresponds with the specimen labeled ATD6-112 (Bermúdez de Castro et al., 2010), a new undocumented tooth has been recorded by using the micro-CT. This new tooth in the TD6.2 fossil hypodigm is the lower right fourth premolar of the ATD6-112 mandible. This tooth is

only represented by the initial formation stage of the buccal cusp enamel (Supplementary Fig. 4). Its mesiodistal diameter measures ~3.4 mm.

The mineralisation stages of the SH hominins were obtained by analyzing high-quality pictures and by directly observing the teeth, whereas H1 and H3 of TD6.2 were inferred by using micro-CT images. The mineralisation stages of H11 were obtained by translating into Demirjian's scale the stages published by Bermúdez de Castro et al. (2010).

Modern Human Reference Samples

Due to some fossil specimens preserved permanent mandibular dentition, other preserved permanent maxillary dentition and one specimen from TD6 preserved both, permanent and deciduous mandibular teeth **(Table 1)**, it was necessary to use different comparative samples to perform different comparisons. The first comparative sample is called "Burgos mandibular I" which was drawn from three different subsets and consists of DMS of mandibular teeth except M3. The third molar was excluded of this sample due to the tempo of development of this tooth, as it is highly variable among modern populations with a high frequency of agenesis. Thus, in a first attempt, we did not include the developmental stage of M3 in the DMS in order to avoid confounding findings due to this effect.

The first subset is composed of 415 cross-sectional standardized orthopantomographs of Spanish children between 4 and 16 years old. These orthopantomographs were chosen from patients attending to different dental clinics to diagnostic and treatment. The inclusion criteria were the following: a) availability of panoramic radiographs with high clarity and good contrast, b) no systemic diseases or craniofacial anomalies, c) normal dental conditions (e.g. no hypodontia, gross pathology and missing mandibular permanent teeth except third molar) and d) no previous orthodontic treatment. The developmental stages of the different teeth were assesed following the system developed by Demirjian et al. (1973). They were first scored by YQ and thus, independently validated by RG-G. The second subset was derived from the data included in the Electronic Encyclopedia on Maxillo-Facial, Dental and Skeletal Development (Demirjian, 1996). These data come from a longitudinal study of French-Canadian children in Montreal, conducted in the 1960s and 1970s. A total of 494 radiographs were utilized from this collection. The inclusion criteria for these radiographs was that at least one tooth was developing. The third subset was selected from a sample of 75 mandibles of subadult individuals from a medieval archaeological population excavated in the Dominican Monastery of San Pablo (Adán-Álvarez, 2003) that are now housed at the Laboratory of Human Evolution of the University of Burgos. These specimens were scanned using a YXLON Compact (YXLON International X-Ray GmbH, Hamburg, Germany) industrial multislice computed-tomography (CT) scanner, located at the University of Burgos. The mandibles were aligned along the long axis of the right mandible corpus. Scanner energy was set at 160KV and 4 mA and the field of view was between 111.1 and 187.5 mm to encompass the entire mandibles. The Mimics™ (Materialise, Belgium) software program was used to visualize the CT images and make the virtual reconstructions. In this sample, the inclusion criteria for these mandibles were that they preserved seven permanent teeth (from I1 to M2) and that at least one of them was developing. In this way, the final sample is composed of 32 mandibles. In this sample, developmental stages of each tooth were scored by RG-G.

The second comparative sample is called "Burgos mandibular II" and consist of 462 cross-sectional standardized orthopantomographs of Spanish children in which at least M3 was developing. This sample was used to explore the effect of the calcification status of this tooth in the differences and analogies between DMS of fossil and modern humans. As in the case of "Burgos mandibular I", the developmental stages of the different teeth were first scored by YQ and thus, independently validated by RG-G.

The third comparative sample is denoted as "Burgos mandibular III" and consist of 24 CT-scans from San Pablo collection in which both permanent and deciduous teeth were preserved. The total sample consist of 24 individuals.

The fourth comparative sample, called "Burgos maxillar" consist of 380 orthopantomographs of maxillary teeth chosen from patients attending to different dental clinics to diagnostic and treatment. The inclusion criteria and assessment of the developmental stages of each tooth were performed in the same way that "Burgos mandibular I". This sample was used in comparison of DMS of fossil specimens with upper dentition preserved.

All the above samples consist of European or European origin populations. Studies comparing African-derived versus European-derived populations have shown differences in the relative calcification of several teeth (Tompkins, 1996b). Thus, differences between DMS of fossil specimens and our reference sample, do not necessarily imply that these DMS are unique of fossil specimens. Taking this into account, in those cases in which we detected differences between DMS of TD6 and SH individuals and our reference sample, we performed an additional comparison of these fossils with other modern human sample. To do that, we used a sample from the University of Bordeaux that consists of 2387 children (1346 girls and 1041 boys) aged from 2 to 16 years. Their geographic origins include Southern France, Iran and the Ivory Coast (see Braga and Heuze (2007) for further details). This reference sample is based on cross-sectional standardized panoramic radiographs of teeth, and children selected were clinically free of anomalies in tooth number, size or shape. Only lower teeth were scored (from I1 to M2), thus, we have only been able to make comparisons between this sample and SH specimens with lower dentition.

Despite these modern human samples are relatively large, we acknowledge that more samples from larger geographic areas and temporal frames should be taken into consideration to have an overall perspective of modern human variation.

Bayesian Statistical Approach

The comparison of the DMS in the *H. antecessor* sample, the Sima de los Huesos hominins, and the samples of modern humans was performed using a Bayesian statistical approach (Braga et al., 2005; Braga and Heuze, 2007), which produces a probability indicating the likelihood that the developmental pattern of a fossil individual may be found within the variation of the modern human population. The underlying hypothesis is that any DMS represents a developmental module. This DMS is composed of hierarchical units, which show varying degrees of interaction. The teeth are, therefore considered as statistically dependent units in the Bayes's rule of conditional probability. As stated previously, the

Bayesian approach integrates the concept of modularity, as opposed to tooth-by-tooth analysis (Braga and Heuze, 2007).

The interactions between teeth can be measured by deconstructing the original DMS into two subsets with no shared elements. Following this approach, each DMS was separated into a finite number of combinations that correspond to the conditional probabilities of observing one or more teeth at a certain developmental stage (subset_1) conditioned on the attained developmental status of the remaining teeth (subset_2) (Braga and Heuze, 2007). This probability can be expressed as follows:

P(subset_1/subset_2) = P(subset_2/subset_1) * Pprior(subset_1) / [P(subset_2/subset_1) * Pprior(subset_1)] + [P(subset_2/subset≠1) * Pprior(subset≠1)]

where:

- P(subset_2/subset_1) is the observed proportion of individuals in the reference samples showing the DMS corresponding to the subset_2 given the DMS corresponding to the subset_1.

- P(subset_2/subset≠1) is the observed proportion of individuals in the reference samples showing the DMS corresponding to the subset 2 given a DMS different to that of subset_1.

- Pprior(subset_1) is the probability that the DMS corresponding to the subset_1 may be found within the references samples.
- Pprior(subset≠1) is the probability that the DMS is different to that of the subset_1 may be found within the references samples.

As can be seen in this formula, the posterior probabilities depends on the prior probabilities. These prior probabilities can be calculated as the relative frequencies of this subset_1 in our reference sample. In this way, we were assuming that our reference samples priors are representative of the fossil individuals. However, the references samples were constructed by "availability sampling". It implies that our reference samples exhibit biased distributions of the different dental maturity stages. Thus, posterior probabilities derived this way will tend to over or underestimate in the fossil individuals. In these cases, the best option is to choose priors by using external knowledge independent of the data (Couvreur et al., 2010). Thus, we have two options to estimate priors: either use demographic data or to assume an unbiased and uniform frequency distribution of the different developmental stages of each teeth (Braga et al., 2005). In this case, we selected the second option, since the posterior probabilities of the different DMS of fossil specimens will be estimated independent of the distribution of the dental maturity stages in the reference samples used in this study **(Boquet-Appel, 1986)**.

Probabilities were classified based on the thresholds of p<0.25 and p>0.75. While values of 0.25 and 0.75 does not represent an absolute cutoff in a continuous probability distribution ranging from 0 to 1, in Bayesian approaches they represent a threshold to assess the likelihood of different events (Braga and Heuze, 2007). In this way, probabilities lower than

0.25 indicate very unlike events, probabilities greater than 0.75 represent very likely events and probabilities between 0.25 and 0.75 are more likely associated to random events.

A final mean probability for each specimen has been calculated as the average of all the conditional probabilities of their different combinations.

Results

DMS from *H. antecessor* from Gran Dolina and the Sima de los Huesos hominins are displayed in Table 1. The *H. antecessor* individual H11 is the least mature of the TD6.2 sample. Hominin H1 is the most mature individual within the *H. antecessor* hypodigm, and hominin H3 has an intermediate state of dental maturity. The individuals XVIII and XXV from Sima de los Huesos have completely formed incisors and first molars, with premolars and second and third molars that are still developing. Hominin XVIII is slightly less mature than hominin XXV, as the former's developing teeth are in an earlier mineralization stage. In fact, the canine roots of the XVIII hominin were still forming when this individual died.

Table 2 shows the distribution of probabilities that the DMS of these fossil specimens falls within our reference sample. The hominin H11 of *H. antecessor* displays the highest probabilities that its DMS falls within the modern human range, when deciduous teeth are both incorporated or excluded, with values above 0.95 (Fig. 2). In the case of H1, which has both lower and upper dentition preserved, the probabilities, when the M3 is excluded, are between 0.73 and 0.83 respectively. However, when the M3 is incorporated in the analysis, the probability of the upper dentition decreases to 0.60, although the probability of the lower dentition is barely altered. The probability of the upper dentition sequence of the H3 specimen when the M3 is excluded is 0.85. However, when the M3 is included, the probability is 0, as this specific pattern of DMS is not present in the modern human sample. Within our reference sample the most frequent dental maturational sequence is that showed by H1 lower dentition (excluding M3), and the less frequent is that showed by H3 upper dentition (including M3). They were found 69 and zero times, respectively.

Regarding SH individuals, within our reference sample the maturational sequences of H-XVIII upper and lower dentition are found 1 and 11 times respectively. For the upper dentition this sequence is found in one male aged 8 years. In the case of the mandibular dentition, we found this DMS in six females aged between seven and nine years and in five males aged between seven and ten years. Interestingly, none of these modern individuals show at the same time the maxillar and mandibular maturational sequence than H-XVIII. The DMS of H-XXV is found one time in our reference simple, in one male aged 11 years.

The probabilities of the upper and lower dentitions of the Sima de los Huesos hominins XVIII and XXV (Fig. 3) when the M3 is included are 0, for the same reason stated above. Interestingly, when M3 is removed, the DMS of SH specimens are compared with Burgos's sample, most of probabilities are lower than 0.25. Thus, we can assume that the DMSs showed by hominins XVIII and XXV are unlikely to occur is in this sample.

Nonetheless, when DMS of SH individuals are compared with Bordeaux's sample, most of probabilities are higher or equal 0.75 (Fig. 3), namely, these sequences are likely in this sample. These differences may be related to inter-populational differences in dental development in *Homo sapiens*. Based on this, we cannot discard that hominins from SH present a pattern of development similar to that of *Homo sapiens*.

However, in some combinations the probabilities showed by hominins from SH are lower than 0.25 relative to both modern samples. In the case of hominin XVIII these combinations correspond to the following conditional probabilities: I1I2M1 if CP3P4M2 and CP3P4M2 if I1I2M1. For the hominin XXV these conditional probabilities are: CM2 if I1I2P3P4M1, P3P4 if I1 I2CM1M2, I1I2CM1M2 if P3P4 and I1I2P3P4M1 if CM2. Therefore, in these sequences the developmental status of one or some teeth deviate significantly from those observed in our two reference samples. We did not observe probabilities lower than 0.25 in the combinations corresponding to the developmental status of each of these teeth taken separately versus the others. Thus, we concluded that none of these teeth separately show an abnormal developmental status in these hominins from SH.

In the case of hominin XVIII the DMS more informative is I1I2M1 if CP3P4M2, since this specimen showed I1, I2 and M1 completely formed. When we fixed in our "Burgos mandibular I" sample the sequence C=F, P3=E, P4=E and M2=E, the developmental stages of I2 and M2 are more delayed. Concretely, a 64% of individulas showed the I2 and M2, respectively, in a developmental stage F or G. This could point to a relative advancement of development of I2 and M2 in this SH specimen.

In the case of hominin XXV, the analysis of sequences CM2 if I1I2P3P4M1and I1I2P3P4M1 if CM2, point to a relative advance in the developmental status of canine and second molar. If we fixed in our "Burgos mandibular I" sample the developmental stages of P3 and P4 as F, a 88% of individuals showed the canine and second mandibular in stages of development more delayed than XXV hominin. The developmental stages of I1, I2 and M1 are equal in our comparative sample then in hominin XXV.

 In the other way, the analysis of sequences P3P4 if I1 I2CM1M2 and I1I2CM1M2 if P3P4 show that P3 and P4 are relatively more advanced in our comparative sample. Fixing the developmental stages of I1, I2, C, M1 and M2 a 82% of individulas within our comparative sample showed a developmental stage H or G.

Thus, it seems that SH hominins could be characterized by a relative advancement of development of M1 and M2 and/or a relative delay in the development of both premolars. Discussion and Conclusion

This study represents the first attempt to apply a Bayesian statistical approach to quantify DMS variation in fossil populations older than Neandertals. Here, we used this method on two extinct hominin populations from the Early and Middle Pleistocene sites at Atapuerca (Spain).

In *H. antecessor*, the DMS of hominin H1 has a high range of probabilities of belonging to a modern human population. However, the DMS of this hominin shows fully developed incisors, canines, premolars and first molars, all at stage H (Table 1). This prevents the evaluation of differences between anterior and posterior teeth during development, as well as the comparison of the developmental pattern with that of modern humans. The high probabilities are due principally to the relative development of the second and third molars, which are still forming. It is also very likely that the DMS of the hominin H11 of the same population, which has the permanent dentition from the I1 to the M1, including the two deciduous molars, is within modern human variation. However, as M2 and M3 are not preserved in this specimen, the comparison between anterior-posterior dichotomy also remains incomplete. Finally, *H. antecessor* H3 does present anterior and posterior teeth that are still forming. In this case, the probabilities vary from 0 to 0.85 depending on the inclusion or exclusion of the M3, respectively. In this regard, *H. antecessor* H3 suffered from a unilateral impactation of the M2 as a result of the ectopic position of the developing M3, likely due to the lack of space in the maxilla (Martín-Francés et al., 2020).

Overall, *H. antecessor* dental development follows modern human patterns when looking at only anterior or posterior teeth separately, and when M3 is excluded. When both regions are compared, the M3 is advanced in its mineralization in respect to modern humans. However the relative development of I1 and M1 fit within the range of modern humans, which corresponds with previous observations (Bermúdez de Castro et al., 1999, 2010).

In respect to the hominins from the Sima de los Huesos site, different probabilities are produced, depending on the modern sample used for comparison, and on the presence of M3 in the analyses. The DMS do not correspond to either modern human sample when the M3 is included, indicating that this tooth is advanced in its relative development when compared to modern humans. When the M3 is removed, the probabilities vary depending on which reference sample of modern humans is used for comparison.

Mandibular third molars are highly variable in their timing of maturation in modern humans (Liversidge, 2008). They also have the highest frequency of polymorphism, malposition, impactation and agenesis (Nanda, 1954; Garn et al., 1963; Anderson et al., 1975; Bermúdez de Castro, 1989). It has been shown that there are statistical differences in the delay of M3 formation in Caucasian children from both London and Cape Town in comparison to black South African children (Liversidge, 2008). This delay is also present in a French-Canadian population compared to black South Africans, in both the second and third molars (Tompkins, 1996b). The delay of molar formation in non-black Africans compared to black Africans might be responsible for the different probabilities in the Sima de los Huesos lower dentition when their mineralisation sequences are compared with modern human variation. The sample from the University of Bordeaux includes individuals of black sub-Saharan provenance, originating from the Ivory Coast, whereas the sample from Univerity of Burgos does not include any. This may be the reason for the apparent similarity between the Burgos sample and the Sima de los Huesos individuals, and the apparently advanced lower molar developmental sequences of the ancient individuals in comparison to the Bordeaux sample.

In a sample of white Americans, it has been observed that the formation of maxillary M3s was slightly advanced in comparison to the mandibular M3s (Mincer et al., 1993). However, this pattern is not shared in either the Sima de los Huesos hominins or the sample of *H. antecessor*. Both M3s of hominin H1 of the Gran Dolina-TD6.2 site are at the same stage of mineralisation (C), whereas the maxillary M3 of the hominin XVIII from Sima de los Huesos is delayed in its formation in comparison to the mandibular M3 (B and C, respectively).

The lower first and second molars of both the *H. antecessor* H1 and the hominin XXV of Sima de los Huesos are at stages H and G, respectively (Table 1). Differences between the hominins from these sites emerge when the premolars and third molars are considered. Premolars in the hominin XXV from Sima de los Huesos are developmentally delayed in comparison to hominin H1 of *H. antecesso*r (stages F-F and H-H, respectively). The third molar, however, is developmentally advanced in XXV in comparison to hominin H1 (stages D and C, respectively). Caucasian French-Canadian, Native American and black African modern human samples do not display differences in their relative premolar calcification across these three groups (Tompkins, 1996b), so differences observed in both Pleistocene hominins could be explained by a taxonomic signal.

As the Burgos sample was used when calculating the probabilities in *H. antecessor* and the hominins from Sima de los Huesos when the M3 is removed, the fact that the Early Pleistocene population has higher probabilities than the Middle Pleistocene indicates that the M2 is relatively advanced in its development in the Sima de los Huesos individuals. This evidence was previously postulated for the XVIII specimen (Bermúdez de Castro and Rosas, 2001).

It was stated that P3 in Neandertals was delayed in comparison to modern humans (Tompkins, 1996a). However some differences emerge with Sima de los Huesos, as in this group both premolars appear to be delayed. Whereas the M2 in Neandertals was advanced in the development compared to modern humans (Tompkins, 1996a), the M2 of Sima de los Huesos displays the opposite behavior. These features could present a taxonomic signal to discern Sima de los Huesos and Neandertals.

Following the Bayesian statistical approach, Neandertals display probability values that exclude them from belonging to modern humans, as shown in the Roc de Marsal (Bayle et al., 2009c) and the Cova del Gegant (Quam et al., 2015) specimens. The Cova del Gegant individual is dated in 52.3 ± 2.3 ka (Daura et al., 2010), whereas the Roc de Marsal Neandertal is located most probably between 60 and 70 ka (Guérin et al., 2012). In both cases, the Bayesian probability is zero, which means that their DMSs are not present in the modern human reference samples employed. The Lagar Velho 1 child, a potential hybrid specimen between Neandertals and anatomically modern humans, with an age of ~24.5 ka B.P. (Duarte et al., 1999), also presents a dental maturation pattern not represented in the modern human variation (Bayle et al., 2010). Interestingly, the Neandertal specimen Spy VI, represented only by four deciduous teeth (lower i1, i2, c; and upper i1), shows a Bayesian probability above 0.75 in respect to modern humans (Crevecoeur et al., 2010). This high probability is not surprising, as it is only based on deciduous incisors and one canine.

It is remarkable that the chronological relationships between anterior and posterior teeth were found to be responsible for differences in extinct hominins (Tompkins, 1996a). This could explain why Neandertals that preserve both types of teeth and the Lagar Velho specimen have a pattern of dental development not present in modern humans, whereas Spy VI, only represented by anterior dentition, shows higher probabilities. In contrast, the Upper Paleolithic child from La Madeleine (LM4), a fully anatomically modern human child with an age of 10,190 ± 100 years (Gambier et al., 2000), shows comparatively higher probabilities of belonging to modern humans (Bayle et al., 2009d). In particular, 30% of LM4 DMS probabilities are superior to 0.75, and 70% fall between 0.25 and 0.75.

The Roc de Marsal child has a relatively advanced stage of mineralization of the first molar in respect to the comparatively delayed maturation levels of its incisors (Bayle et al., 2009c). Bearing in mind that the relative development of I1 and M1 in *H. antecessor*, and very likely that of the Sima de los Huesos hominins, is within modern human variation, this asynchrony in the Neandertals I1/M1 relative development could be interpreted as exclusive to *H. neanderthalensis*. Therefore, this feature may be key to differentiating Upper Pleistocene Neandertals from their ancestors in the European Middle Pleistocene.

El Sidrón J1 Neandertal preserves the permanent dentition from I1 to M2 and some deciduous teeth (Rosas et al., 2017). Only the M3 crypt is present so that its relative stage of mineralization with respect to the modern human sample employed in this study remains unknown. However, the DMS of this specimen is not found in any of the 10901 modern humans radiographs used to calculate probability density plots. From a non-Bayesian approach, probability density plots for mean age of transition entering each individual permanent tooth stage indicate that El Sidrón J1 fell within the modern human range. However, premolar and molar plots show slightly older, advanced, ages than anterior dentition plots in respect to the modern human sample, although a high degree of overlap exists among both fields.

H. antecessor hominin H3 has an upper M2 at stage D as does El Sidrón lower M2. However, the upper M3 is already at stage B in H3 but is not yet mineralizing in El Sidrón. Similarly, SH XVIII M2 and M3 are just two developmental stages apart (E and C) while M2 and M3 in El Sidrón are at least four stages apart (M2 stage D, M3 crypt only present). This all suggests a Neandertal DMS distinct from modern humans as well as greater advancement of M3 relative to M2 in TD6.2 and SH hominins than in El Sidrón. However, other Neandertal specimens reveal the likely extent of variation in M1-M2-M3 mineralization sequence. When molar formation stages are expressed as M1 H, M2 F and M3 C in Scladina (Smith et al., 2010), then M2 and M3 are just two stages apart and comparable to individual XXV from SH. This both fits with the range of more advanced or delayed chronological ages determined for Neandertals at various stages of development (Macchiarelli et al., 2006; Smith et al., 2010; Rosas et al., 2017) but also underscores the likely developmental overlap between the TD6.2, SH and Neandertal hominins.

Lateral enamel formation timing of the entire dentition in both *H. antecessor* and the Sima de los Huesos hominins was ~27% shorter than in modern humans (Modesto-Mata et al., 2020). Despite the high probability of some dental mineralization sequences of *H. antecessor* and Sima de los Huesos in respect to modern human variation, the fact that both

populations display an advanced molar development and more rapid enamel formation times, distinguishes them from *H. sapiens*.

These two different lines of evidence shed some light on the processes of growth and development in *H. antecessor* and the Sima de los Huesos hominins. They support a working hypothesis that both Pleistocene populations had a period of general growth, ontogeny and skeletal maturation most likely at the more advanced end of the modern human distribution today. Although more data are needed to further test this hypothesis, such as accurate estimations of the timing and rate of root formation, cuspal enamel formation times and ages at eruption in these hominins, some findings about skeletal development seem to confirm it. For instance, clavicular growth and development in *H. antecessor* is faster than in modern humans (García-González et al., 2009), a trait shared with *H. neanderthalensis* and *H. ergaster*. Some evidence points to a slower height growth rate in Neandertals during infancy and early childhood compared to modern humans, which would explain differences in adult height between these populations (Martín-González et al., 2012). However, this fact explains differences in the growth rate models but not in the overall timing of maturation. In modern humans, dental development and skeletal growth are moderately correlated and thus, individuals that are dentally advanced relative to their peers also tend to be skeletally advanced (Šešelj, 2013). Thus, if we can assume the same relationship between dental and skeletal development in *H. antecessor* and modern humans, these findings, along to those of this study, suggest an advanced development in *H antecessor*.

In conclusion, both *H. antecessor* and the Sima de los Huesos hominins show advanced development of the M3 in comparison to modern *H. sapiens*. However, the Sima de los Huesos hominins appear also to show advanced development of the M2 in respect to both *H. antecessor* and modern humans. When anterior and posterior dentitions of *H. antecessor* are compared independently with modern humans, they present high probabilities of statistical variation. However, when both anterior and posterior teeth are compared synchronously, their probabilities decrease, indicating differences between the developing anterior and posterior dentitions between modern and extinct human populations. This study confirms that it is the chronology and sequence of M2 and M3 development in hominins that likely best reflects the overall period of ontogeny.

Acknowledgments

Tables and Figures

Table 1: **Mineralization stages of *H. antecessor* (TD6.2) and Sima de los Huesos (SH) teeth following stages defined by Demirjian et al. (1973) for permanent dentition and Liversidge and Molleson (2004) for deciduous dentition**. These stages were employed in the Bayesian statistical approach to determine whether their sequences belong to *H. sapiens*. brk = broken.

Table 2: **Mean Bayesian probabilities of the Gran Dolina (TD6.2) specimens (H1, H3, H11) and Sima de los Huesos (SH) hominins (XVIII, XXV) in respect to the DMS variation in modern human variation**. Mean probabilities [p(mean)] and standard deviations [p(sd)] are shown. Percentage of combinations displaying values of probability below 0.25 (%p < .25), above 0.75 (%p > 0.75) and between both values (0.25 < %p < .75). Two reference modern human samples (Ref.) are included: University of Bordeaux (BOR) and University of Burgos (UBU). M3 and dm represent the inclusion (Yes) or the exclusion (No) of the M3 and deciduous molars, respectively, in the calculations of the mean bayesian probabilities. Position is either lower (L) or upper (U).

Fig. 1: Buccal view of the complete dentition of the Sima de los Huesos hominin XVIII. Top row: upper dentition; bottom row: lower dentition. dm2s are placed above the crown of their respective P4s. Top left: upper right M3; bottom right: lower left M3. Scale bar = 1 cm.

Fig. 2: **Bayesian probabilities of the *H. antecessor* dental sequences in respect to the DMS variation in modern humans**. Three hominins are depicted: H1, H3, H11. A) lower dentition of H1; B) upper dentition of H1; C) upper dentition of H3; D) lower dentition of H11. Green bar: probabilities equal to or higher than 0.75; red bar: probabilities equal to or lower than 0.25. Red lines and dots: probabilities calculated by using the modern human reference sample from the University of Burgos.

Fig. 3: **Bayesian probabilities of the Sima de los Huesos (SH) dental sequences in respect to the DMS variation in modern humans**. Two hominins are represented: XVIII and XXV. The M3 has not been included in the calculation of the Bayesian probabilities for both specimens. A) lower dentition of hominin XVIII; B) lower dentition of hominin XXV; C) upper dentition of hominin XVIII. Green bar: probabilities equal to or higher than 0.75; red bar: probabilities equal to or lower than 0.25. Red lines and dots: probabilities calculated by using the modern human reference sample from the University of Burgos; blue lines and dots in respect to the reference sample from University of Bordeaux.

Supplementary Materials

Supplementary Tables

Supplementary Table 1: **Teeth from the two Sima de los Huesos hominins employed in the calculations of the Bayesian probabilities in respect to the DMS variability in modern humans**. Hominins: XVIII and XXV. Position (U = upper; L = lower); side (L = left; R = right).

Supplementary Table 2: *Homo antecessor* **(TD6.2) teeth employed in the calculations of the Bayesian probabilities in respect to the DMS variability in modern humans**. Three hominins from TD6.2 have been analysed: H1, H3 and H11. Position (U = upper; L = lower); side (L = left; R = right)

Supplementary Figures

Supplementary Fig. 1: Buccal view of the lower dentition of the Sima de los Huesos hominin XXV. dm2s are placed above the crown of their respective P4s. From left to right: right M3 to left M3. Scale bar = 1 cm.

Supplementary Fig. 2: Partially transparent micro-CT images of the buccal view of the preserved teeth of the Gran Dolina H1 specimen. Images not a scale.

Supplementary Fig. 3: Partially transparent micro-CT images of the buccal view of the preserved teeth of the Gran Dolina H3 specimen. Images not a scale.

Supplementary Fig. 4: **Microcomputerised axial tomographies of the two lower right premolars of the *H. antecessor* hominin 11**. (b) buccal; (o) occlusal; (l) lingual; (d) distal. Two scales: 5 mm.

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