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Testing the inhibitory cascade model in the Middle Pleistocene Sima de los Huesos (Sierra de Atapuerca, Spain) hominin sample

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Abstract

The Middle Pleistocene Sima de los Huesos (SH) site has yielded more than 7.500 human fossil remains belonging to a minimum of 29 individuals. Most of these individuals preserve either the complete mandibular molar series or at least the first (M_1) and second (M_2) molars. The inhibitory cascade mathematical model was proposed by Kavanagh *et al*. (Nature, 449, 427–433 [2007]) after their experimental studies on the dental development of murine rodent species. The activator–inhibitor mechanism of this model has shown its ability for predicting evolutionary size patterns of mammalian teeth, including hominins. The main aim of this study is to test whether the size molar patterns observed in the SH hominins fit the inhibitory cascade model. With this purpose, we have measured the crown area of all SH molars in photographs, using a planimeter and following techniques used and well contrasted in previous works. Following one of the premises of the inhibitory cascade model, we expect that the central tooth (M_2 in our case) of a triplet would have the average size of the two outer teeth. The absolute difference between the observed and the expected values for the M_2s ranges from 0.23 to 8.46 mm^2 in the SH sample. In terms of percentage, the difference ranges between 0.25% and 10.34%, although in most cases, it is below 5%. The plot of the estimated M_3/M_1 and M_2/M_1 size ratios obtained in the SH hominins occupies a small area of the theoretical developmental morphospace obtained for rodent species. In addition, the majority of the values are placed near the theoretical line which defines the relationship predicted by the inhibitory cascade model in these mammals. The values of the slope and intercept of the reduced major regression obtained for the SH individuals do not differ significantly from those obtained for rodent species, thus confirming that the size of the molars of the SH hominins fits the inhibitory cascade model. We discuss these results in terms of dental development. Despite the promising results in the SH sample, we draw the attention to the fact that most Early Pleistocene *Homo* specimens exhibit a pattern ($M_1 < M_2 > M_3$), which is outside the expected theoretical morphospace predicted by the inhibitory cascade model. The shift from the M1 < M2 < M3 size relationship observed in early hominins

(including *H. habilis*) to the M1 > M2 > M3 size relationship, which is predominant in modern humans, includes sequences that depart from predictions of the inhibitory cascade model. Additional studies are required to understand these deviations.

KEYWORDS

human evolution, inhibitory cascade model, molar size, Sierra de Atapuerca, Sima de los Huesos

1 | INTRODUCTION

Several theories have been put forward to explain the biological mechanisms that regulate the size and morphology of mammalian teeth, and in particular that of hominins (Butler, 1939; Dahlberg, 1945, 1951; Osborn, 1978; Brook, 1984; Sharpe, 1995; Jernvall and Thesleff, 2000; Salazar-Ciudad and Jernvall, 2002; Mitsiadis and Smith, 2006). Butler (1939) proposed the concept of morphogenetic fields. According to this author, the size and morphology of teeth would be modulated by the concentration of certain substances or signals in the embryonic tissues of the oral cavity (Butler, 1939). Dahlberg (1945, 1951) adapted the theory of morphogenetic fields to the human dentition. In his clonal theory, Osborn (1978) proposed the existence of preprogrammed cells that would induce the dental lamina to form a certain dental class. This theory includes the concept of inhibition so that the regions surrounding the clone cells would prevent the formation of other teeth until the migration clone has moved on adequately. At the molecular level, Sharpe (1995) postulated the existence of a homeobox odontogenic code, which would explain the beginning of the different kinds of dental types. This code would be regulated by molecular signals expressed by specific groups of homeobox genes. According to some authors (Brook, 1984; Mitsiadis and Smith, 2006), the three proposals may be compatible.

Based on experimental studies of mouse molars developed in culture, Kavanagh *et al*. (2007) proposed the inhibitory cascade model to explain how development governs relative size and number of post-canine teeth in mammals. According to this model, molar activator/inhibitor ratio is responsible for the size of subsequently developing molars (Kavanagh *et al*., 2007). Whereas the activation mechanism is principally considered to be of mesenchymal origin, the developing molars would produce signaling molecules that inhibit the development of subsequent buds. Kavanagh *et al*. (2007) found that absolute size was independent of the inhibitory cascade in the mouse-derived model. The genotypic–phenotypic relationship between molar position and molar size was defined by the expression:

$$y = 1 + \left[(a - i)/i\right](x - 1)$$

where y is the relative molar size estimated from occlusal area, x is the place of the molar in the molar series, and a and i are the relative strength of the activation and inhibition, respectively. In addition, Kavanagh *et al*. (2007) postulated that selection for diet, an important ecological factor, might be behind the inhibitory cascade-influenced phenotypic changes in mammals. This hypothesis was further validated by Polly (2007) in another 35 mammalian species.

Subsequently, Evans *et al*. (2016) applied this model to hominins focusing on the lower primary teeth (deciduous molars and permanent molars). These authors found that, in contrast to mice, size and proportions were linked in hominins. Whereas *Ardipithecus*, *Australopithecus*, and *Paranthropus* exhibit the M1 > M2 > M3 size relationship, irrespective of overall dental size, in the *Homo* species, there is a close relationship between absolute M_1 size and the relative tooth size. Thus, small M_1 size in *H. sapiens* would produce disproportionately reduced M_3S(Evans *et al*., 2016).

The hominin sample recovered from the Middle Pleistocene site of the Sima de los Huesos (SH, Sierra de Atapuerca, Spain) is characterized by the small size of their post-canine teeth, similar to that of modern humans, and the concomitant reduction and/or loss of the talon/talonid cusps (Bermúdez de Castro, 1988; Bermúdez de Castro and Nicolás, 1995; Martinón-Torres *et al*., 2012). These features were proposed as a clear evidence against the relationship between post-canine teeth reduction and cooked-food diet (Bermúdez de Castro and Nicolás, 1995).

The study of the SH site and fossils suggests that all SH hominins belong to the same biological population (e.gBermúdez de Castro, 1993; Arsuaga *et al*., 1997a; Arsuaga *et al*., 2014). A large number of SH individuals ($n = 18$) preserve the three mandibular molars. Here, we aim to test the inhibitory cascade model in the SH population molar series, as well as to explore the predictions of the inhibitory cascade model in other *Homo* groups.

2 | THE SH SITE

Recent chronological studies provided an age range estimation for the SH hominins between 427 ± 12 ka and 448 ± 15 ka (Arnold *et al*., 2014; Arsuaga *et al*., 2014; Demuro *et al*., 2019). The U-series dating of a cave raft speleothem deposited directly on the hominin cranium 4 from LU-6 yielded a mean age of 434 + 36/−24 kyr (Arsuaga *et al*., 2014). More recently, Demuro *et al*. (2019) provided a mean age of 448 ± 15 ka based on both new single-grain TT-OSL ages for LU-5 and LU-6, and a Bayesian age-depth model built with published PIR-IR and TT-OSL chronologies from the level LU6 (Arnold *et al*., 2014). The combined modeled ranges revealed that the

hominin-bearing layer (LU-6) was deposited between 455 ± 17 ka and 440 ± 15 ka. These dates are consistent with the early-to-mid Middle Pleistocene age for the faunal assemblage recovered from the hominin level (Cuenca-Bescós *et al*., 1997; García *et al*., 1997; Arsuaga *et al*., 2014). Therefore, the SH hominins can be attributed either to MIS 11 or most probably to MIS 12 (Lisiecki and Raymo, 2005).

The SH hominins were first assigned to the species *Homo heidelbergensis* (Arsuaga *et al*., 1997b). However, Arsuaga *et al*. (2014) recently excluded the SH hominins from this taxon due to the absence of Neanderthal-derived features in the Mauer mandible, the holotype of *H. heidelbergensis*. Previous studies on different anatomical elements identified several derived Neanderthal features in the SH hominins (e.gArsuaga *et al*., 1993; Bermúdez de Castro, 1993; Carretero *et al*., 1997; Martínez and Arsuaga, 1997; Arsuaga *et al*., 1997a; Rosas, 2001; Martinón-Torres *et al*., 2012; Arsuaga *et al*., 2014). Later, the DNA analysis confirmed the close relationship between the SH hominins and Neanderthals (Meyer *et al*., 2016). Currently, the specific taxonomic allocation of SH hominins is under revision.

3 | MATERIALS AND METHODS

The SH hominin collection comprises more than 7.500 human fossil remains belonging to a minimum of 29 individuals (J.M. Bermúdez de Castro, personal observation in the SH hominin assemblage). The SH dental sample includes a total of 45 M_1s, 44 M_2s, and 45 M_3s. The three molars (right and/or left series) are present in 18 individuals. Individual V was excluded from this study due to the extreme dental wear (degree 6 of the Molnar classification [1971]). In order to test the inhibitory cascade model, we have used the triplet of the permanent lower molars (M_1, M_2, and M_3) of these individuals. In addition, there are six additional individuals that preserve both the M_1 and the M_2 whereas thirteen isolated M_3s cannot be assigned to any of the 29 identified individuals. If the inhibitory cascade model is supported with our data, it should be possible to test whether the isolated M_3s belongs to any of the identified individuals in which the M_3 is missing.

Although Evans *et al*. (2016) employed the crown computed area (CCA = mesiodistal dimension × buccolingual dimension), we preferred to apply the measured crown area (MCA) proposed by Wood and Abbot (1983). We found that the CCA gives a good approximate estimation of the crown area when molars are rectangular. However, in cases where molars (in particular the M_3s) have different shapes (triangular, ovoid, and oval; see Figures 1 and 2), the CCA does not provide a good approximation of the crown area. Each specimen was oriented so that the occlusal plane was perpendicular to the optical axis of a camera fitted with an AF Micro-Nikkor 105 mm, f/2.8D. In order to get a maximum depth of field, an aperture of f/32 was set. The magnification ratio was adjusted to 1:1, and a scale was included in each photograph and placed parallel to the occlusal plane (Figure 2). The occlusal plane and the surface of the scale were arranged so that they were at approximately the same plane. Prints of the specimens were made at ×5 – ×7, a suitable magnification for using a planimeter (Tamaya, Planix 10S). The boundaries of the crown were marked with ink on the photographs following the criteria of Wood *et al*. (1983). The original mesial and distal borders affected by interproximal wear were reconstructed taking as reference the overall crown shape and the buccolingual extent of the wear facets (Wood and Abbot, 1983). Before obtaining any measurement, the exact enlargement of each print was checked and the X = Y scale was entered in the planimeter. Measurements were obtained in mm^2. Each specimen was measured five times by the same author (JMBC), and the mean value was used. We checked the precision of the measurements using the coefficient of variation (CV) of the five measurements. In all cases, the CV ranged between 0.003 and 0.0004 (that is between 0.3% and 0.04% of error). This procedure is time-consuming, but the great accuracy compensates for the effort. Due to the curvature of the mesial, distal, buccal, and lingual faces, the maximum area in occlusal view is located about half the height of the crown, so only a remarkable occlusal wear (e.g., grade 6 of the Molnar classification[, 1971]) affects the measured crown area.

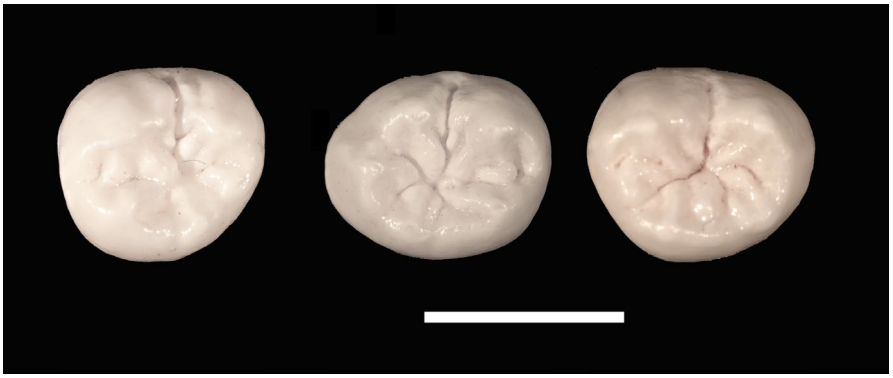

FIGURE 1 Some M_3s of the SH dental sample showing different shapes. From left to right: AT-222, AT-598, and AT-1959. Note the absence of hypoconulid and the reduction of the entoconid in AT-222 and AT-1959. The crown computed area (CCA) is obtained as the multiplication of the mesiodistal (MD) diameter by the buccolingual (BL) diameter (CCA = MD × BL). This measure gives us an approximation to the crown area only when the shape of the crown is rectangular.

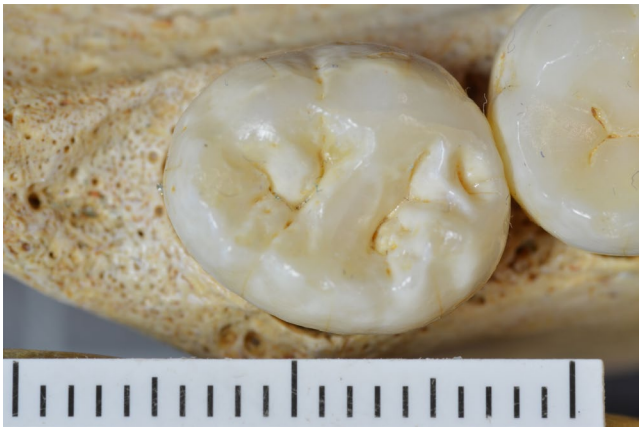

FIGURE 2 Occlusal aspect of the left M_3 of the mandible AT-300 (Individual XII). The aperture of f/32 allows a wide depth field, so a large part of the crown height is well focused.

Following the premise of the inhibitory cascade model, the central tooth of a triplet would be the average size of the two outer teeth (Evans *et al*., 2016). Therefore, we have estimated the expected area of the M_2s of the 17 individuals with the three molars as follows:

$$M_2\text{Area} = (M_1\text{Area} + M_3\text{Area})/2, \text{ or simplifying the expression, } M_2 = (M_1 + M_3)/2$$

The expected values were compared with the observed values, and we obtained the difference between the two values in absolute and relative (percentage) terms.

The standard M_1-M_3 cascade of the SH hominins was tested against the murine inhibitory cascade model. Specifically, we employed the M_3/M_1 and M_2/M_1 ratios in order to include the SH values in the developmental morphospace generated by these two variables. When both the right and left molar series were present, we chose the left side.

Using the R software, *lmodel2* package, we applied the reduced major axis (RMA) regression to explore the correlations between relative occlusal areas. In this package, the RMA states for ranged major axis, which is a different statistical analysis, and the reduced major axis regression is called standard major axis (SMA) regression (Legendre and Legendre, 1998; Queen *et al*., 2002). We applied the RMA instead of ordinary least squares (OLS) because the variable represented on the x-axis (M_2/M_1) is measured with error and also because the RMA is symmetric, meaning that a single line defines the bivariate relationship, regardless of which variable is X and which one is Y (Smith, 2009), like in the inhibitory cascade model. The data were bootstrapped 1000 times, and the resulting regression was compared with the inhibitory cascade model described for murines. Confidence intervals of both the slope and the intercept were obtained from the RMA for the SH sample. If the confidence intervals include the 2.0 slope and −1.0 intercept predicted by the murine inhibitory cascade model, we considered that the SH regression was fitting that obtained for murines.

In addition, and following Evans *et al*. (2016), we calculated the expected area of the M3 in those individuals lacking this tooth as follows:

$$M_2 = (M_1 + M_3)/2; 2M_2 = M_1 + M_3; 2M_2 - M_1 = M_3$$

4 | RESULTS

Table 1 shows the values of the measured crown area for the permanent molars of those individuals that preserve the three molars and the individuals that only preserve the M_1 and M_2. The size relationship obtained for the SH permanent molars is as follows:

$M_1 \approx M_2 \approx M_3$: Individuals XII, XX, XXI, XXII, XXIII, and XXVII (35.3%).

$M_1 \approx M_2 > M_3$: Individuals I, XVIII, and XXV (17.6%).

$M_1 > M_2 > M_3$: Individuals IV, VI, VII, XVI, XIX, XXIV, and XXVIII (41.2%).

$M_1 > M_2 \approx M_3$: Individual XV (5.9%)

Furthermore, in those cases where the M_3 was absent, we observed the following size relationship for the M_1 and M_2:

$M_1 \approx M_2$: Individual XXVI (45.4%)

$M_1 > M_2$: Individuals II, III, X, and XXIX (54.5%)

The average molar size of the SH dental sample is small and similar to that of a recent human population (Bermúdez de Castro and Nicolás, 1995). The size reduction is accompanied by the reduction and/or loss of main cusps. In M_1s, the hypoconulid is absent in 2 out of 23 individuals (8.7%). For the M_2, the hypoconulid is absent in 11 out of 23 individuals (47.8%). Moreover, this cusp is absent in the M_3s of 5 out of the 17 individuals (29.4%) with the complete molar series and in 6 out of the 13 unassigned M_3s. Finally, in 5 M_3s, the entoconid is very small and the tooth displays a triangular occlusal shape (see Figure 2).

In Table 2, we present the expected values for the measured crown area of the M_2s in those individuals with the three molars. The absolute difference between the observed and the expected values ranges from 0.23 to 8.46 mm^2. In the majority of cases, the observed value was greater than the expected value. The differences ranged from 0.25% to 10.34%, although in most cases these differences were less than 5%. This percentage was surpassed only in individual I (7.37% for the right side), individual XVIII (7.61% for the left side), and individual XXV (10.34% for the right side).

When we plot the M_3/M_1 and M_2/M_1 size ratios, we see that all SH individuals occupy a small area of the developmental morphospace (Table 3, Figure 4). Moreover, the majority of the individuals are placed near the theoretical line that defines the relationship predicted by the inhibitory cascade model in rodents, in which the slope is 2.0 and the intercept is −1.0 (Kavanagh *et al*., 2007). The RMA regression of the M_2/M_1 (x) and M_3/M_1 (y) variables in the SH hominin sample gives the following values: slope = 2.08; intercept = −1.12, and r = 0.68 (r^2 = 0.46). The 95% confidence intervals of the RMA for the SH values were (−2.08, −0.46) for the

TABLE 1 Measured crown area (in mm^2) of the permanent molars of 23 of the 29 individuals identified so far in the hypodigm of the Sima de los Huesos site

Individual	Specimen number	Molar	Side	Measured crown area
I	AT-1	M1	Right	103.50
	AT-1	M2	Right	101.22
	AT-1	M3	Right	85.19
	AT-1	M1	Left	102.71
	AT-1	M2	Left	95.45
	AT-1	M3	Left	77.31
II	AT-2	M1	Right	101.53
	AT-142	M2	Right	93.22
	–	M3	Right	**84.91**[a]
III	AT-101	M1	Right	93.66
	AT-271	M2	Right	82.12
	–	M3	Right	**70.58**[a]
	AT-22	M1	Left	88.97
	AT-273	M2	Left	84.32
	–	M3	Left	**79.67**[a]
IV	AT-5369	M1	Right	96.15
	AT-250	M2	Right	91.26
	AT-811	M3	Right	83.26
	AT-14	M1	Left	98.44
	AT-250	M2	Left	90.99
	AT-100	M3	Left	84.52
VI	AT-1759	M1	Left	92.57
	AT-75	M2	Left	86.53
	AT-75	M3	Left	79.72
VII	AT-1957	M1	Right	118.27
	AT-1957	M2	Right	114.73
	AT-13	M3	Right	107.75
X	AT-556	M1	Left	89.54
	AT-169	M2	Left	80.19
	–	M3	Left	**70.84**[a]
XII	AT-300	M1	Right	101.25
	AT-300	M2	Right	104.10
	AT-300	M3	Right	97.59
	AT-300	M1	Left	99.01
	AT-300	M2	Left	101.25
	AT-300	M3	Left	100.56
XIV	AT-2276	M1	Right	99.61
	AT-284	M2	Right	86.13
	–	M3	Right	**72.65**[a]
	AT-1459	M1	Left	100.92
	AT-2272	M2	Left	87.81
	–	M3	Left	**74.70**[a]
XV	AT-2193	M1	Right	90.78
	AT-2193	M2	Right	83.62

(Continues)

TABLE 1 (Continued)

Individual	Specimen number	Molar	Side	Measured crown area
	AT-2193	M3	Right	81.25
XVI	AT-2779	M1	Right	94.19
	AT-2763	M2	Right	90.89
	AT-3182	M3	Right	87.14
XVIII	AT-943	M1	Right	102.65
	AT-1752	M2	Right	97.93
	AT-2271	M3	Right	94.58
	AT-829	M1	Left	100.38
	AT-941	M2	Left	103.22
	AT-2277	M3	Left	84.18
XIX	AT-576	M1	Left	82.77
	AT-505	M2	Left	75.37
	AT-505	M3	Left	68.73
XX	AT-3175	M1	Right	109.85
	AT-3890	M2	Right	104.65
	AT-4138	M1	Left	107.99
	AT-946	M2	Left	104.87
	AT-6695	M3	Left	98.37
XXI	AT-888	M1	Right	92.03
	AT-888	M2	Right	92.40
	AT-888	M3	Right	93.64
XXII	AT-605	M1	Right	103.47
	AT-605	M2	Right	103.60
	AT-605	M3	Right	106.33
	AT-605	M1	Left	103.86
	AT-605	M2	Left	108.29
	AT-605	M3	Left	106.68
XXIII	AT-607	M1	Right	92.44
	AT-607	M2	Right	95.49
	AT-607	M3	Right	91.56
	AT-607	M1	Left	95.32
	AT-607	M2	Left	93.14
	AT-607	M3	Left	92.41
XXIV	AT-2438	M1	Right	89.32
	AT-2438	M2	Right	**69.20**[b]
	AT-2438	M3	Right	72.30
	AT-1458	M1	Left	91.79
	AT-2396	M2	Left	83.99
	AT-2385	M3	Left	74.08
XXV	AT-3933	M1	Right	94.67
	AT-3889	M2	Right	90.23
	AT-3943	M3	Right	69.47
	AT-3934	M1	Left	92.09
	AT-6579	M2	Left	89.57
	AT-6580	M3	Left	70.92

(Continues)

TABLE 1 (Continued)

Individual	Specimen number	Molar	Side	Measured crown area
XXVI	AT-561	M1	Right	88.72
	AT-1756	M2	Right	88.62
	–	M3	Right	**88.52**[a]
	AT-1775	M1	Left	88.92
	AT-2270	M2	Left	88.57
	–	M3	Left	**88.22**[a]
XXVII	AT-792	M1	Left	102.76
	AT-3176	M2	Left	102.01
	AT-792	M3	Left	100.54
XXVIII	AT-950	M1	Right	108.02
	AT-950	M2	Right	98.54
	AT-950	M3	Right	80.60
	AT-950	M1	Left	106.50
	AT-950	M2	Left	98.06
	AT-950	M3	Left	83.72
XXIX	AT-272	M1	Right	85.99
	AT-1761	M2	Right	79.72
	–	M3	Right	**73.45**[a]
	AT-286	M1	Left	85.51
	AT-557	M2	Left	78.56
	–	M3	Left	**71.61**[a]

[a]Bold value indicates estimated values (not real).

[a]Expected value according to the prediction of the inhibitory cascade model.

[b]This tooth exhibits a development anomaly.

intercept and (1.4, 3.08) for the slope. Therefore, our observed values do not differ significantly from those obtained by Kavanagh *et al*. (2007) for rodent species.

Table 4 shows the data obtained from the isolated M_3s that are not assigned to any of the individuals identified so far in the SH hypodigm. Under the premise of the inhibitory cascade model, at least three individuals (X, XIV, and XXIX) from the SH collection should have small third molars with a measured crown area of around 70 mm^2. Only two out of thirteen specimens, AT-599 (right) and AT-2760 (left), which belong to the same individual, have a measured crown area of about 70 mm^2.

5 | DISCUSSION AND CONCLUDING REMARKS

The inhibitory cascade model was experimentally conceived in murine rodent species as an activator–inhibitor network-derived model, capable of predicting evolutionary paths of the size of the post-canine dentition in a given selective environment (Kavanagh *et al*., 2007). This model has inspired several works, which have sought to test their predictions or explain the variability of some dental features (Halliday and Goswami, 2013; Schroer and Wood, 2015). According to Halliday and Goswami (2010, p. 9), "*the Inhibitory Cascade Model is plesiomorphic to Mammalia as a whole*." The inhibitory cascade development system would also be the plesiomorphic state for Old World primates, whose relative molar size is expressed as M1 < M2 < M2 (Schroer and Wood, 2015). Evans *et al*. (2016) applied the inhibitory cascade model to hominins and concluded that variation in tooth crown size and proportions follows a simple rule, which allows precise predictions about the size of permanent and deciduous post-canine teeth. In the genera *Ardipithecus*, *Australopithecus*, and *Paranthropus*, the molar size relationship tends to be M1 < M2 < M3, with proportions that are constant regardless of overall dental size, whereas in the genus *Homo*, the relative size varies with their overall size, and there is a trend toward the M1 > M2 > M3 size pattern.

Given its relative large size and degree of completeness, the Middle Pleistocene SH dental collection provides a unique opportunity for testing the inhibitory cascade model. We analyzed a total of 17 individuals with the complete molar series as well as 13 unassigned M_3S. We employed the MCA instead of the CCA to obtain more accurate dimensions, especially in molars with different shapes.

The results obtained in SH individuals fit perfectly within the inhibitory cascade model. Moreover, the values (slope and intercept)

TABLE 2 Observed and expected values of the measured crown areas of the M_2s. Following the premise of the inhibitory cascade model, the M_2s should have a dimension equal to the average of the two outer teeth

Individual	Side	M2: Observed value (mm^2)	M2: Expected value (mm^2)	Absolute difference (mm^2)	Relative difference, in percentage
I	Right	101.22	94.34	6.88	7.37
I	Left	95.45	90.01	5.44	6.04
IV	Right	91.26	89.70	1.56	1.74
	Left	90.99	91.48	−0.49	0.53
VI	Left	86.53	86.27	0.26	0.30
VII	Right	114.73	113.01	1.72	1.52
XII	Right	104.10	99.42	4.68	4.70
	Left	101.25	99.78	1.47	1.47
XV	Right	83.62	86.01	−2.39	2.77
XVI	Right	90.89	90.66	0.23	0.25
XVIII	Right	97.93	98.38	−0.45	0.46
	Left	103.22	95.92	7.30	7.61
XIX	Left	75.37	75.75	−0.38	0.50
XX	Left	104.87	103.18	1.69	1.63
XXI	Right	92.03	92.83	−0.80	0.86
XXII	Right	106.33	105.05	1.28	1.22
	Left	108.29	105.37	2.92	2.47
XXIII	Right	95.49	92.00	3.49	3.79
	Left	93.14	93.86	−0.72	0.76
XXIV	Left	83.99	82.93	1.06	1.27
XXV	Right	90.23	81.77	8.46	10.34
	Left	89.57	81.50	8.07	9.90
XXVII	Left	102.01	101.65	0.36	0.35
XXVIII	Right	98.54	94.31	4.23	4.48
	Left	98.06	95.11	2.95	3.10

of the RMA regression of the variables M_2/M_1 and M_3/M_1 for the hominins of SH are very close to those obtained by Kavanagh *et al.* (2007) for rodent species. According to these authors (p. 430), "*The inhibitory cascade can be formalized as a simple high-level model in which a balance between activation and inhibition results in equal-sized molars (M1 ≈ M2 ≈ M3) and inhibition has a cumulative effect on the posterior teeth giving a distinct M1 > M2 > M3 pattern.*" In the SH hominin sample, the size relationships $M_1 \approx M_2 \approx M_3$, $M_1 \approx M_2 > M_3$, and $M_1 > M_2 > M_3$ are the most common patterns, whereas the size relationships $M_1 \approx M_2$ and $M_1 > M_2$ show a similar prevalence (see Results). With these data, we can conclude that in SH permanent molars there was a balance between activation and inhibition. In addition, we see that the cumulative effect of inhibition, which causes the reduction of the M_3, is more frequent than predicted by the model. This is the case of the right and left molar series of individuals I and XXV, and the left molar series of the individual XVIII. In these hominins, we observe the size pattern $M_1 \approx M_2 > M_3$, where the M_3 is remarkably reduced with respect to the M_1 and the M_2. According to Evans *et al.* (2016, p. 479), "*…increased intraspecific variation in* Homo *species could also result from relaxed selection, implicated by the increased fluctuating asymmetry found in most* Homo *dentitions compared with australopiths and great apes…*". This hypothesis could also explain the case of individual XVIII from SH, where the size difference between the right and the left M_3 is remarkable.

For the present study, we have used the left molar series of individual XXIV. The size of the right M_2 AT-2438 (Individual XXIV) is particularly small in relation to the M_1 and M_3 and also regarding the left M_2 of the same individual (Table 1). It seems that this tooth suffered a local disturbance during the morphodifferentiation stage of the tooth development that affected not only its size but also its shape. This is reflected by the formation of an evaginatus odontoma (Figure 3). The study of this anomaly in AT-2438 is in progress.

There is disagreement in the analysis of the relationship between cusp number and tooth size. While there are studies that suggest that there is no clear relationship between both aspects (Malhotra and Richardson, 1981; Grine, 1981), previous works (Dahlberg, 1961; Garn *et al.*, 1966) concluded that the absence of the main cusps in modern populations implies a significant decrease in size compared to teeth that preserve the main five cusps. Recent studies showed that the mesial cusps of the upper molars are relatively more stable

TABLE 3 Data used in the RMA regression analysis

Individual	M_1 area	M_2 area	M_3 area	M_2/M_1	M_3/M_1
I	102.72	95.45	77.31	0.93	0.75
IV	98.44	90.99	84.52	0.92	0.86
VI	92.57	86.53	79.72	0.93	0.86
VII	118.27	114.73	107.75	0.97	0.91
XII	99.01	101.25	100.56	1.02	1.01
XV	90.78	83.62	81.25	0.92	0.89
XVI	94.19	90.89	87.14	0.96	0.92
XVIII	100.38	103.22	84.18	1.03	0.83
XIX	82.77	75.37	68.73	0.91	0.83
XX	107.99	104.87	98.37	0.97	0.91
XXI	92.03	92.40	93.64	1.00	1.02
XXII	103.86	108.29	106.68	1.04	1.03
XXIII	95.32	93.14	92.41	0.98	0.97
XXIV	91.79	83.99	74.08	0.91	0.81
XXV	92.09	89.57	70.92	0.97	0.77
XXVII	102.76	102.01	100.54	0.99	0.98
XXVIII	106.50	98.06	83.72	0.92	0.78

TABLE 4 Measured crown area of the isolated M_3S of the SH dental sample, in mm^2. Specimens AT-30 and AT-1473 exhibit an occlusal wear of grade 2, according to the Molnar classification (1971). The other specimens show incompletely developed roots and were unerupted (degree of wear 1 of the Molnar classification, 1971)

Specimen number	Molar	Side	Measured crown area
AT-30	M3	Right	85.58
AT-143	M3	Right	89.35
AT-222	M3	Right	88.13
AT-598[a]	M3	Left	89.99
AT-599[b]	M3	Right	70.89
AT-942	M3	Right	90.48
AT-1945	M3	Left	79.12
AT-1959	M3	Right	86.36
AT-1468[a]	M3	Right	89.89
AT-1473	M3	Left	87.63
AT-2273	M3	Left	81.88
AT-2760[b]	M3	Left	68.99
AT-2777	M3	Left	86.94

[a]These teeth belong to the same individual.

[b]These teeth belong to the same individual.

FIGURE 3 Occlusal aspect of the M_2 AT-2438 (Individual XXIV), showing a possible evaginatus odontoma and an abnormal size reduction regarding the M_1 and the M_3. This tooth was not included in the present analyses.

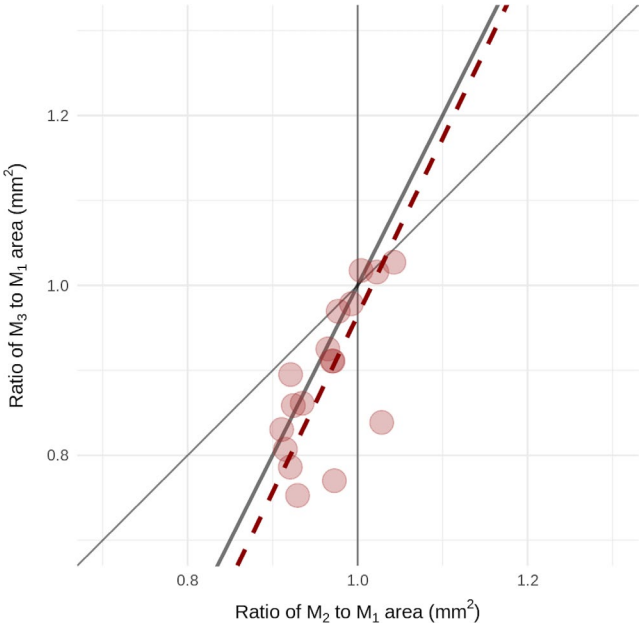

FIGURE 4 Plot of the values M_2/M_1 vs. M_3/M_1 in the SH molar dental sample in the developmental morphospace defined by these variables. The thick gray line plots the function $y = 1 + [(a-i)/]\ (x-1)$, and it matches the prediction of Kavanagh *et al.* (2007) for rodents. The thin gray lines include the 95% confidence interval of this function. The dashed red line represents the RMA regression of the M_2/M_1 and M_3/M_1 variables in the SH sample, and the red circles represent each one of the SH individuals. Note that most of the red circles are near the gray line predicted by Kavanagh *et al.* (2007) for rodents and show the trend to the $M_1 > M_2 > M_3$ size pattern in the SH hominins. Furthermore, the majority of the SH individuals are within the 95% confidence interval of the inhibitory cascade model. However, it is also interesting that a significant number of individuals are placed at the intersection where $M_2/M_1 = M_3/M_1 = 1$. See Kavanagh *et al.* (2007), Polly (2007), and Schroer and Wood (2015) for further explanations.

than the distal cusps and that there is a statistically significant relationship between the overall size decrease in the mandibular molars and a greater reduction of the talonid in modern humans (Yamada and Brown, 1988; Macho and Moggi-Cecchi, 1992; Bermúdez de Castro, 1993; Bermúdez de Castro and Nicolás, 1995). Similarly, a reduction of the number of cusps (and particularly the talonid cusps) implies a reduction of the overall size of the molars in fossil hominis (Wood and Abbott, 1983; Bermúdez de Castro and Nicolás, 1995). Other

studies have tested predictions of the patterning cascade model (Jernvall and Jung, 2000) regarding the relationship between accessory cusp presence and crown size in humans (Hunter *et al*., 2010), chimpanzees (Skinner and Gunz, 2010), and hominins (Ortiz *et al*., 2018). In addition, these papers find that larger teeth are more likely to exhibit central accessory cusps (e.g., cusp 6), but are only likely to exhibit peripheral accessory cusps (e.g., Carabelli cusp) when they also have smaller distances (reflecting smaller inhibitory zones) between their principal cusps. It is well known that the calcification of the cusps in primate molars occurs in an orderly sequence, the hypoconulid being the last cusp to calcify (Kraus, 1963; Swindler, 1985). For instance, a reduction in the number of cells of the mesenchyme below certain thresholds could produce the loss of certain elements (cusps) and the spatial reorganization of the remaining elements (see Alberch and Gale, 1985). Thus, the loss of hypoconulid is followed by the loss of the entoconid or the hypoconid in an ordered manner. If we consider the premises of the inhibitory cascade model, inhibitors could affect the ability of the molars to complete their formation influencing development of the enamel knots. Although the activators would promote the formation of a molar, the chances of ending up in a complete phenotype, at least with the five main cusps, would be reduced. It is interesting to note that the small size dimension of the crown of the SH molars regarding other contemporaneous hominins is accompanied by the concomitant loss of the hypoconulid and the reduction of the entoconid in some M_3 s.

Although Kavanagh *et al*. (2007) proposed that there are some molecules capable of promoting the formation of teeth, such as BMPs, activin A, and ectodysplasin, the precise genetic basis of the inhibitory cascade model remains to be identified. Moreover, mutations or reduction of gene dosage of Pax9, a member of the paired box (PAX) family of transcription factors, has been also related to congenitally missing teeth (Kist *et al*., 2005; Bonczek *et al*., 2017). These changes in the expression of a certain gene could be added to the presence of inhibitors predicted by the inhibitory cascade model, thus achieving exaggerated reduction or the absence of the third molar. According to this model, M_3S are missing when the size of the M2 falls below the half size of the M1 (Kavanagh *et al*., 2007). Indeed, if the size of the M2 is less than half the size of M1, the value of the size of M3 would be negative in the expression M3 = 2 M2–M1. In addition, it is interesting to remember that in *H. sapiens*, and perhaps in other late species of the genus *Homo*, the beginning in the formation of the M3s experiences a considerable delay with respect to the formation of the M2s (e.g., Dean and Cole, 2016). This delay, which may be considered a developmental heterochrony (see Alberch *et al*., 1979, and Bermúdez de Castro, 1989), could have helped to neutralize the signal that activates the formation of the third molar.

On the other hand, Evans *et al*. (2016) concluded that the M1 < M2 < M3 size pattern remained constant in Plio-Pleistocene hominins (*Ardipithecus*, *Australopithecus*, and *Paranthropus*) irrespective of overall dental size, whereas "*…near the origin of the genus Homo, a change in the scaling relationship between m1* [M1] *size and inhibitory cascade patterning occurs…*" (Evans *et al*., 2016, p. 478). At some point throughout hominin evolution, the size relationship shifted from the constant M1 < M2 < M3 molar size sequence observed in early hominins to the M1 > M2 > M3 sequence, which is the most frequent pattern in modern humans. This shift, probably due to a decrease in mesenchymal activation (Evans *et al*., 2016), could help to clarify the transition from the genus *Australopithecus* to the genus *Homo*. In this sense, the growing molar series of the permanent molars in *H. habilis* represents another biological feature that, together with the time of development of the teeth and their possible implications in the life history pattern (e.gBromage and Dean, 1985; Smith, 1989), would favor the inclusion of *H. habilis* in the genus *Australopithecus*, as proposed by Wood and Collard (1999). Similarly, Evans *et al*. (2016) quote the case of the specimen D2600 from Dmanisi, which resembles the pattern of *Australopithecus*, whereas the other specimens from this site follow the *Homo* pattern. Interestingly, previous works on the Dmanisi dentognathic evidence (Skinner *et al*., 2006; Bermúdez de Castro *et al*., 2014) suggested the possibility of two different taxa represented at the Dmanisi site.

Nevertheless, it is important to remember that the $M_1 < M_2$ size pattern is not unusual in the genus *Homo*. Thus, this pattern is observed in specimens such as KNM-ER 992, KNM-WT 15000, ATD6-5, and ATD6-96 from Atapuerca Gran Dolina-TD6, all of them from the Early Pleistocene, as well as in Mauer, Arago 2, Arago 13, Montmaurin-La Niche, Thomas I, Tighenif 1, or Tighenif 2 (Middle Pleistocene). Furthermore, the trend toward the reduction of the M_3 appeared very early in the genus *Homo*, as it is evinced in D211 from Dmanisi, ATD6-96, Mauer, Arago 2 and 13, Thomas 1, or in Tighenif 1, 2, and 3 (see Bermúdez de Castro *et al*. (1999) and references therein). As illustrated in Figure 4, the hominins of SH show the change toward the $M_1 > M_2$ pattern, but still present a high percentage of individuals in which $M_1 \approx M_2$, the first step, whereas the reduction of the M_3 already appears well defined in these hominins. The size pattern M1 < M2 > M3 observed in many of the Early Pleistocene *Homo* specimens requires a combination of low inhibition and early arrest of the M3 development (see Kavanagh *et al*., 2007). Future studies should explore how this size relationship can be understood within the inhibitory cascade model (Evans *et al*., 2016). In particular, it is important to establish when and how these changes occurred. From this evidence, we can conclude that all these changes did not occur during the transition from the genus *Australopithecus* to *Homo*, but this shift happened gradually over a longer period of time.

Finally, this study provides a new criterion for the dental assignment of isolated teeth. During decades, we have progressively estimated the minimum number of individuals (MNI) based on metric and morphological criteria (e.g., Bermúdez de Castro *et al*., 2004). Using the inhibitory cascade model, we have hypothesized that the antimeres AT-599 and AT-2760 (two isolated M3s) could be potentially assigned to individuals X, XIV, and XXIX. In addition, we ruled out the assignment of the remaining isolated M3s, as they have a significantly larger area than AT-599 and AT-2760. The predictive nature of the inhibitory cascade model could help to assign teeth to specific individuals.

In summary, although the data obtained in the present work for SH fit the inhibitory cascade model, more research is necessary to

explain the variability observed in the relative size of the molars during the entire evolution of the genus *Homo*. In particular, it is important to understand the shift from a primitive M1 < M2 < M3 size pattern to the more variable and derived pattern (M1 > M2 > M3) found in later *Homo*. This derived pattern includes a first step with reduction of the M3 s, followed by a reduction of the M2s. The frequent M1 < M2 > M3 size relationship observed in the Early Pleistocene hominins requires further research (see Evans *et al*., 2016).

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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