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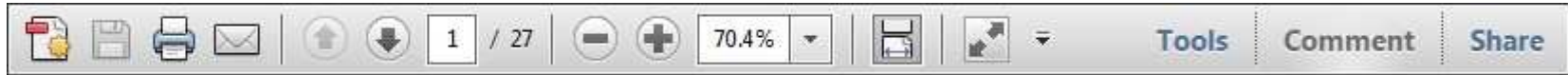
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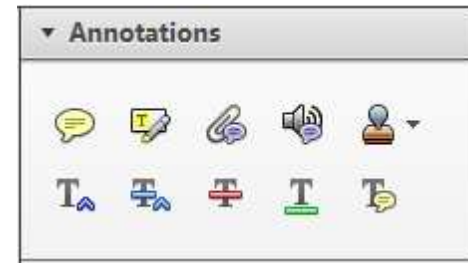
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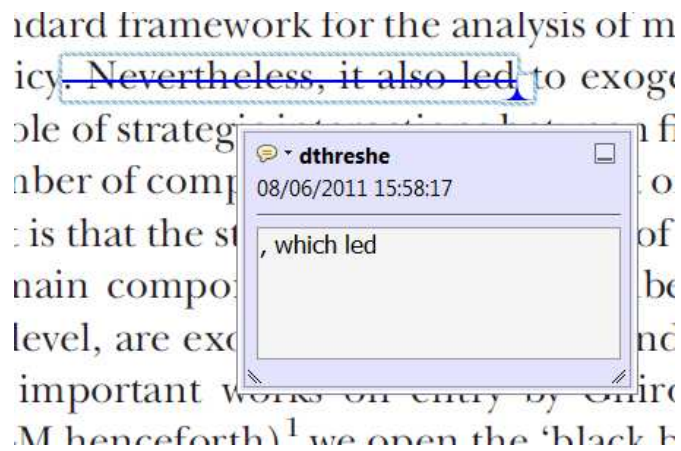
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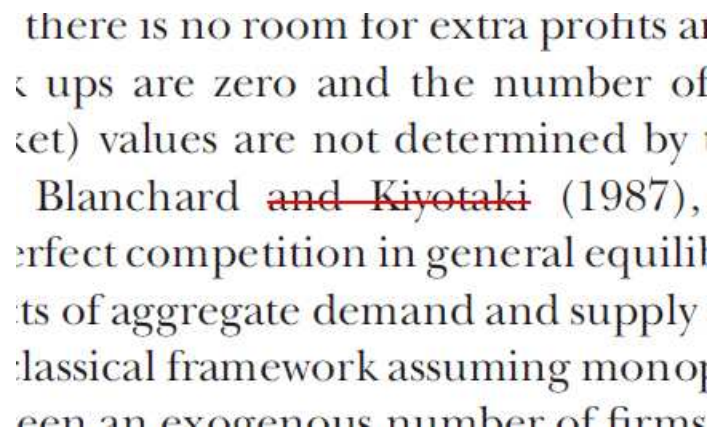
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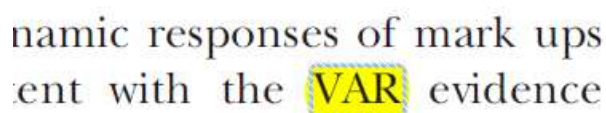
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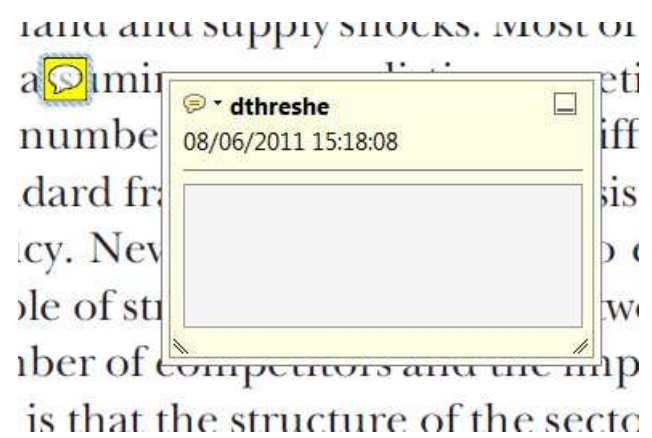
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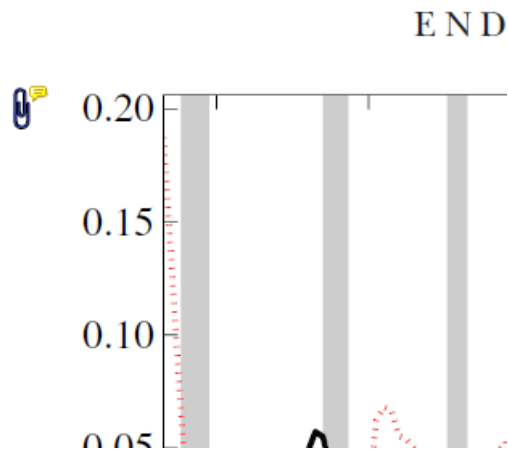
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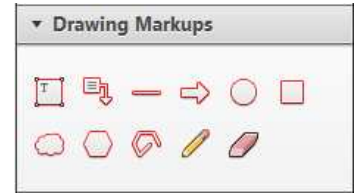
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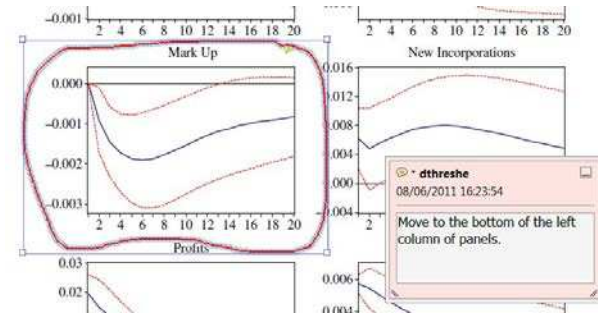
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RESEARCH ARTICLE

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Trabecular architecture in the thumb of Pan and Homo: implications for investigating hand use, loading, and hand preference in the fossil record

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Abstract

Objectives: Humans display an 85–95% cross-cultural right-hand bias in skilled tasks, which is considered a derived behavior because such a high frequency is not reported in wild non-human primates. Handedness is generally considered to be an evolutionary byproduct of selection for manual dexterity and augmented visuo-cognitive capabilities within the context of complex stone tool manufacture/use. Testing this hypothesis requires an understanding of when appreciable levels of right dominant behavior entered the fossil record. Because bone remodels *in vivo*, skeletal asymmetries are thought to reflect greater mechanical loading on the dominant side, but incomplete preservation of external morphology and ambiguities about past loading environments complicate interpretations. We test if internal trabecular bone is capable of providing additional information by analyzing the thumb of *Homo sapiens* and *Pan*.

Materials and methods: We assess trabecular structure at the distal head and proximal base of paired (left/right) first metacarpals using micro-CT scans of *Homo sapiens* ($n = 14$) and *Pan* ($n = 9$). Throughout each epiphysis we quantify average and local bone volume fraction (BV/TV), degree of anisotropy (DA), and elastic modulus (E) to address bone volume patterning and directional asymmetry.

Results: We find a right directional asymmetry in *H. sapiens* consistent with population-level handedness, but also report a left directional asymmetry in *Pan* that may be the result of postural and/or locomotor loading.

Conclusion: We conclude that trabecular bone is capable of detecting right/left directional asymmetry, but suggest coupling studies of internal structure with analyses of other skeletal elements and cortical bone prior to applications in the fossil record.

KEYWORDS

biomechanics, hand evolution, hominin behavior, microstructure, skeletal asymmetry

1 | THE EVOLUTION OF HAND PREFERENCE AND HANDEDNESS

Handedness is a lateralized behavior that refers to the consistent, preferential use of either the right- or left-hand across skilled manipulative tasks (Marchant & McGrew, 2013; McGrew & Marchant, 1997).

A right-hand bias is frequently reported in humans to be between ~85% and 95% cross-culturally, and thus is considered a population-level behavior (Faurie, Schiefenhover, Le Bomin, Billiard, & Raymond, 2005). Being that many functional asymmetries are now recognized across vertebrates, (Cowell, Waters, & Denenberg, 1997; Frühholz et al., 2015; Indersmitten & Gur, 2003; Lewis, Phinney, Bredczynski-Lewis, &

46 DeYoe, 2006; Roth, Lora, & Heilman, 2002; Tate, Fischer, Leigh, & Ken-
47 drick, 2006; Weiss, Ghazanfar, Miller, & Hauser, 2002), we understand
48 such biases to be widespread and ancient (Andrew & Rogers, 2002).
49 While the genetic determinants of handedness remain elusive, genome-
50 wide association studies support heritability for hand preference in
51 humans (Armour, Davison, & McManus, 2014; McManus, Davison, &
52 Armour, 2013) and chimpanzees (*Pan troglodytes*) (Hopkins, Reamer,
53 Mareno, & Schapiro, 2015).

54 In contrast to humans, observational studies of individual hand
55 preference in other primates have determined that variation in posture
56 (Braccini, Lambeth, Schapiro, & Fitch, 2010; Dodson, Stafford, For-
57 sythe, Seltzer, & Ward, 1992; Olson, Ellis, & Nadler, 1990), task com-
58 plexity (Bardo, Pouydebat, & Meunier, 2015; Byrne & Byrne, 1991;
59 Hopkins, 1995), and terrestriality (Marchant & McGrew, 2007; Miller &
60 Paciulli, 2002) all have an impact on the strength of hand preference.
61 While chimpanzees do demonstrate a consistent preference across
62 tasks at an individual level (Marchant & McGrew, 2013), a group/species
63 level side-bias remains unobserved in the wild (e.g., Boesch, 1991;
64 McGrew & Marchant, 1992) and only weakly present in captive popu-
65 lations (~65% right directional asymmetry) (e.g., Hopkins et al., 2011;
66 Tabiowo & Forrester, 2013). Although the latter point speaks to a
67 potential capacity (Hopkins, 2013), confounding factors in captive popu-
68 lations—such as task transmission through human observation
69 (Marchant & McGrew, 2013)—suggest that species level right-hand
70 preference evolved following the panin-hominin split (Corballis, 2003),
71 and potentially only within *Homo* (Lozano, Mosquera, Bermúdez de
72 Castro, Arsuaga, & Carbonell, 2009; Uomini, 2011).

73 In response to these observations, many have proposed that the
74 species-level right directional asymmetry in humans coevolved with (1)
75 an intensified reliance upon increasingly complex stone tool manufac-
76 ture/use from at least ~2.6 Ma (Semaw et al., 2003; Steele, 2004;
77 Steele & Uomini, 2005) to possibly ~3.3 Ma (Harmand et al., 2015),
78 and with (2) selection for a highly dexterous hand working in conjunc-
79 tion with an augmented suite of visuo-cognitive functional asymme-
80 tries (Cantalupo, Freeman, Rodes, & Hopkins, 2008; Fitch & Braccini,
81 2013; Hopkins, 2013; Meguerditchian, Vaclair, & Hopkins, 2010;
82 Steele & Uomini, 2005; Stout & Chaminade, 2012; Stout, Toth, Schick,
83 & Chaminade, 2008). Testing these proposed cause and effect relation-
84 ships in this coevolution model hinges largely on the timing of when
85 hand preference became fixed in past populations (Steele, 2004; Ube-
86 laker & Zarenko, 2012; Uomini, 2009). Archaeological techniques for
87 addressing this question rely on right/left directional asymmetries in
88 the production of rock-art stencils of the hand (Faurie & Raymond,
89 2004), or signs of striking preference during stone flake tool production
90 (Rugg & Mullane, 2001; Toth, 1985; but see Ruck, Broadfield, & Brown,
91 2015) and use (Phillipson, 1997). The value of such analyses is appa-
92 rent, but their interpretive power is limited by time-averaging, the
93 sparse availability of examples at the onset of the archaeological
94 record, and their disassociation from a specific individual/group/species
95 (Cashmore, Uomini, & Chapelain, 2008). Other techniques, such as
96 skeletal analysis, suffer from missing and incomplete remains, but pro-
97 vide information on individual and group-level preference by detecting

consistent morphological departures from normal right/left symmetry 98
(Auerbach & Ruff, 2006; Van Valen, 1962) that are beyond the random 99
fluctuating asymmetries resulting from environmental stress (Palmer, 100
1994). Such directional bias has been observed in striations accruing 101
from meat cut between clenched incisors (Bermúdez de Castro, Brom- 102
age, & Jalvo, 1988; Frayer et al., 2012; Lozano et al., 2009) and asym- 103
metrical bone remodeling in response to frequent loading of the 104
humeri on the dominant side (Volpato et al., 2012). 105

1.1 | Bone functional adaptation, loading, and handedness 106

Bone's tendency to remodel in response to the mechanical environ- 108
ment—broadly referred to as bone functional adaptation (Currey, 2003) 109
—is best explained by the mechanostat model (Frost, 1987), which 110
holds that bone mass is regulated by the continual removal and 111
renewal of strain-damaged bone. Biomechanically, morphological varia- 112
tion in both cortical (Bass et al., 2002; Shaw, 2011; Stock, 2006) and 113
trabecular bone (Lambers et al., 2013; Morgan et al., 2015; Schulte 114
et al., 2013) strongly correlates with the loading environment (Christen 115
et al., 2014). Within tubular bones, the most frequently observed corre- 116
lation is found in variation of cross-sectional geometry at the mid-shaft 117
(Marchi, 2005; Ruff, Holt, & Trinkaus, 2006; Ruff & Jones, 1981), which 118
is thought to remodel in a way that confers greater resistance to bend- 119
ing and torsion (but see Demes et al., 1998; Wallace, Judex, & Demes, 120
2015; and below). Similarly, *in vivo* studies analyzing homologous vol- 121
umes of interest (VOI) of trabeculae at the epiphysis (e.g., Barak, Lie- 122
berman, & Hublin, 2011; Mitra, Rubin, & Qin, 2005; Pontzer et al., 123
2006) demonstrate that differences in loading regimes results in 124
changes to the orientation, thickness, connectivity, spacing, and overall 125
distribution of this structure (e.g., Lambers et al., 2013; Reznikov, 126
Chase, Brumfeld, Shahar, & Weiner, 2015). This variation in trabecular 127
structure allows joint reaction forces to be efficiently transferred away 128
from the articular surface and into the cortices (Currey, 2003; Keaveny, 129
Morgan, Niebur, & Yeh, 2001; Lieberman, Devlin, & Pearson, 2001; 130
Rafferty & Ruff, 1994). 131

Following this model, biomechanical studies focusing on variation 132
in osseous tissue have advanced our understanding of the interrela- 133
tionships among habitual behavior, locomotion, and loading environ- 134
ments for extant (Fajardo & Müller, 2001; Marchi, 2005; Ryan & 135
Ketcham, 2002b; Ryan & Krovitz, 2006; Ryan & van Rietbergen, 2005; 136
Ryan & Walker, 2010; Stock & Pfeiffer, 2001) and extinct primates 137
(Barak et al., 2013; Ryan & Ketcham, 2002a; Trinkaus, Churchill, & 138
Ruff, 1994). Studies applying this perspective to questions of hand 139
preference frequently report a right directional asymmetry in mechani- 140
cal resistance of the upper limbs (Barros & Soligo, 2013; Churchill & 141
Formicola, 1997; Macintosh, Pinhasi, & Stock, 2014; Shaw, Hofmann, 142
Petraglia, Stock, & Gottschall, 2012; Trinkaus et al., 1994;) and manual 143
remains (Lazenby, 1998; Lazenby, Cooper, Angus, & Hallgrímsson, 144
2008; Mays, 2002; Roy, Ruff, & Plato, 1994; Singh, 1979) of past 145
human populations that are commensurate with group/species-level 146
right handedness. Such departures from right/left symmetry are 147
thought to be the byproduct of frequent lateralized loading on the 148

149 dominant side (Auerbach & Ruff, 2006; Kanchan, Mohan Kumar, Pra-
150 deep Kumar, & Yoganarasimha, 2008), which is supported by studies of
151 uni-manual loading and self-reported hand preference in living athletes
152 (Bass et al., 2002; Shaw, 2011).

153 Despite such results, the relationship between behavior and bone
154 functional adaptation is not always straightforward. For example, varia-
155 tion in primate trabecular structure of different skeletal elements does
156 not always correlate well with predicted loading based on locomotor
157 behavior because of high intragroup variation or substantial overlap
158 across different locomotor groups (e.g., Fajardo, Müller, Ketcham, &
159 Colbert, 2007; Maga, Kappelman, Ryan, & Ketcham, 2006; Ryan &
160 Shaw, 2012; Schilling et al., 2013). Furthermore, Shaw and Ryan (2012)
161 found a consistent biomechanical signal in the cross-sectional geometry
162 and trabecular architecture of the primate humerus but not in the
163 femur. Such disagreement is consistent with Stock, Shirley, Sarringhaus,
164 Davies, and Shaw (2013) who found that levels of right directional
165 asymmetry in the paired humeri and second metacarpals differed
166 across medieval, industrial, and hunter-gatherer populations. Of these
167 groups, the hunter-gatherer group showed a much stronger right direc-
168 tional asymmetry in the humerus (83.6%) compared with second meta-
169 carpal (62.5%) (Stock et al., 2013). Although many of these studies do
170 uphold an interpretation of some response to loading, it is clear that
171 the mechanisms underlying bone functional adaptation are not fully
172 understood (Currey, 2012) and that many other factors may contribute
173 to changes in bone morphology.

174 Indeed, debate exists about the potential systemic impact on other
175 areas of the skeleton when one bone/region is loaded (Cresswell, Goff,
176 Nguyen, Lee, & Hernandez, 2016; Lieberman, 1996; Sample et al.,
177 2008; Sugiyama, Price, & Lanyon, 2010; Wallace et al., 2010), and how
178 bone remodeling changes in response to differences in age (Nikander
179 et al., 2010; Pearson & Lieberman, 2004; Ruff et al., 2006), muscle
180 (Robling, 2009) versus joint reaction loading (Judex & Carlson, 2009;
181 Schipilow, Macdonald, Liphardt, Kan, & Boyd, 2013), force (Christen
182 et al., 2014; Schulte et al., 2013), and even how these factors are bal-
183 anced against the role of the bone in maintaining homeostasis (Currey,
184 2003). Beyond this, large scale genetic studies have identified inde-
185 pendent loci for cortical and trabecular bone that are associated with
186 higher risk of fracture (Paternoster et al., 2013; Yerges et al., 2010),
187 which suggests certain fixed aspects to bone morphology that may be
188 insensitive to loading. Similarly, investigations into the question of
189 changes to bone density during hormonal osteoporotic intervention
190 make it clear that the cellular response of the boney matrix is sensitive
191 to physiological agents that might act to augment, nullify, or buffer the
192 reaction to loading (Bahtiri et al., 2015; Xhae et al., 2015). Such com-
193 plexities are highlighted in a recent study by Wallace et al. (2015) who
194 used three cohorts of treadmill-exercised mice to clarify the relation-
195 ship of peak-load and bone functional adaptation. In this study it was
196 shown that although peak forces were greater in the forelimbs, only
197 the hindlimbs of the exercised mice reflected meaningful cortical and
198 trabecular skeletal adaptation, which, the authors suggested, could be
199 explained by a non-uniform response of the cells responsible for bone
200 growth and repair. In light of this, it is clear that new methods for

201 detecting variances in bone morphology must be added to pre-existing
202 ones to refine our understanding of the relationship between behavior,
203 loading environment, function, and skeletal response (Cashmore et al.,
204 2008; Lazenby, 2002; Steele, 2004).

205 With recent advances in computational power it is now feasible to
206 analyze multiple VOIs (Su, Wallace, & Nakatsukasa, 2013) or the entire
207 internal trabecular structure (Gross, Kivell, Skinner, Nguyen, & Pahr,
208 2014) to gain a greater understanding of how trabecular bone varies
209 throughout an epiphysis or bone. The latter method allows the map-
210 ping of site-specific bone volume to total volume (BV/TV) and degree
211 of anisotropy (DA) values onto a 3D tetrahedral mesh, thus facilitating
212 the visual comparison of quantitative data. This is valuable because
213 BV/TV is consistently shown to be the strongest predictor of fracture
214 resistance (Keaveny et al., 2001; Maquer, Musy, Wandel, Gross, &
215 Zysset, 2015; Stauber, Rapillard, van Lenthe, Zysset, & Müller, 2006),
216 and understanding this site-specific distribution has already proven val-
217 uable in interpreting joint loading position related to locomotion and
218 manual behavior in extant (Tsegai et al., 2013) and extinct (Skinner
219 et al., 2015) primate hand bones. Furthermore, recent studies inspect-
220 ing the localized nature of trabecular repair support the view that for-
221 mation and remodeling sites correspond to areas of load (Christen
222 et al., 2014; Cresswell et al., 2016; Schulte et al., 2013), which supports
223 the idea of visualizing and describing this site-specific variation. If
224 applied to bones of the hand, this method has strong potential rele-
225 vance for reconstructing hominin manipulatory repertoires and the
226 evolution of hand preference in the fossil record.

1.2 | Thumb loading and predictions 227

228 In humans many complex manual tasks utilize pinch, key, or power
229 grips that are facilitated by a long thumb relative to the fingers (Ladd,
230 Crisco, Hagert, Rose, & Weiss, 2014; Marzke, 1997; Napier, 1960; Sus-
231 sman, 1979). Such grips are important during stone tool manufacture
232 and use (Marzke et al., 1998) and often involve forceful opposition pro-
233 vided by a derived set of thenar and pollical muscles that allows the tip
234 of the thumb to flex while the base remains extended (e.g., when hold-
235 ing a needle) (Diogo, Richmond, & Wood, 2012; Marzke et al., 1999).
236 Experimental studies have shown that during tool-related activities,
237 loading of the thumb of the dominant hand is high (Rolian, Lieberman,
238 & Zermeno, 2011; Williams, Gordon, & Richmond, 2012) compared
239 with non-dominant thumb (Key & Dunmore, 2015). This differs from
240 other great apes, such as Pan, that possess a short and comparatively
241 weaker thumb (Marzke et al., 1999), and most often use less forceful
242 pad-to-side precisions grips (Marzke & Wullstein, 1996; but see
243 Marzke, Marchant, McGrew, & Reece, 2015) that are employed during,
244 for example, nut-cracking (Boesch & Boesch, 1993) and ant-fishing
245 (Marchant & McGrew, 2007). Because of such differences in anatomy
246 and use between humans and other apes, the thumb remains the focus
247 of multidisciplinary attempts to ascertain its biomechanical role (Cheema,
248 Cheema, Tayyab, & Firoozbakhsh, 2006; Key & Lycett, 2011; Marzke
249 et al., 1998) and evolutionary change over time (Diogo et al., 2012;
250 Niewoehner, 2001, 2006; Niewoehner, Weaver, & Trinkaus, 1997;
251 Shrewsbury, Marzke, Linscheid, & Reece, 2003; Smith, 2000; Tocheri

TABLE 1 Average BV/TV, DA, and elastic modulus in the study sample

Variable	Pan pairs (n = 9)				Homo pairs (n = 14)				Pan (mean L&R)		Homo (mean L&R)		Between groups	
	L	SD	R	SD	L	SD	R	SD	Mean	SD	Mean	SD	U	p Value
BV/TV head, %	34.74	(6.10)	32.65	(5.19)	20.18	(4.44)	22.44	(2.80)	33.69	(5.60)	21.31	(3.34)	716	<0.01
BV/TV base, %	27.12	(3.84)	26.83	(4.53)	16.86	(3.33)	18.96	(2.66)	26.74	(4.06)	17.91	(2.78)	714	<0.01
DA head	1.04	(0.11)	1.00	(0.01)	1.28	(0.17)	1.29	(0.17)	1.02	(0.06)	1.29	(0.11)	88	<0.01
DA base	1.22	(0.25)	1.14	(0.17)	1.30	(0.15)	1.34	(0.18)	1.18	(0.20)	1.32	(0.15)	76	<0.01
E head	3.36	(1.13)	3.01	(1.00)	1.50	(0.52)	1.82	(0.32)	3.19	(1.06)	1.66	(0.37)	708	<0.01
E base	2.40	(0.72)	2.28	(0.819)	1.17	(0.37)	1.43	(0.31)	2.34	(0.75)	1.30	(0.31)	708	<0.01

Abbreviations (BV/TV = bone volume; DA = degree of anisotropy; E = elastic modulus in gigapascals; L&R = mean value of the mean (right and left sides) values; L = mean value of all left metacarpals; R = mean value of all right metacarpals; SD = standard deviation; U = Mann-Whitney U score; p = exact p value for Mann-Whitney U test). Shaded boxes indicate left directional asymmetry.

et al., 2003; Tocheri, Orr, Jacofsky, & Marzke, 2008; Trinkaus & Villemeur, 1991; Villemeur, 1994; Vlček, 1975; see Almécija, Alba, & Moya-Sola, 2012; Almécija, Wallace, Judex, Alba, & Moya-Sola, 2015 for a view that certain features of the thumb are retained from Miocene apes).

To this end, we investigate trabecular architecture and directional asymmetry in the thumb of recent *Homo sapiens* and *Pan* to assess if such an analysis might be applied to questions of loading history and hand preference within the fossil record. Given the predictions of the mechanostat model (Currey, 2003; Frost, 1987), variation in loading of the thumb should be reflected in the first metacarpal (Mc1) because the pollical musculature passes along the base and head to attach at the phalanges (Brand & Hollister, 1993; Maki & Trinkaus, 2011; Marzke et al., 1998; Trinkaus & Villemeur, 1991), meaning this bone will be loaded both by joint reaction forces and muscular tension during flexion and opposition (Hu, Ren, Howard, & Zong, 2014; Kargov, Pylatiuk, Martin, Schulz, & Doderlein, 2004; Pataky, Slota, Latash, & Zatsiorsky,

2012). We predict that the *H. sapiens* first metacarpals will experience asymmetric loading reflecting group-level hand preference, while *Pan* should reflect no group bias. Although highly lateralized terrestrial galloping has been reported (Arcadi & Wallauer, 2011), the thumb is not loaded during terrestrial knuckle-walking (Matarazzo, 2013; Sarringhaus, MacLatchy, & Mitani, 2014; Wunderlich & Jungers, 2009). Potentially high and variable loading of the thumb is thought to occur during arboreal climbing, suspensory locomotion (Hunt, 1991, 1994; Marzke & Wullstein, 1996), and grips observed during feeding (Marzke et al., 2015), behaviors for which individuals can show a hand preference. However, the lack of directional asymmetry in a previous study of trabecular architecture of paired first, second, and fifth metacarpals of *Pan troglodytes* (Lazenby, Skinner, Hublin, & Boesch, 2011) suggest the same will be true for the first metacarpal in the present study.

Accordingly, we predict that (1) the BV/TV distribution and overall architectural trabecular pattern of the Mc1 will reflect variation in the

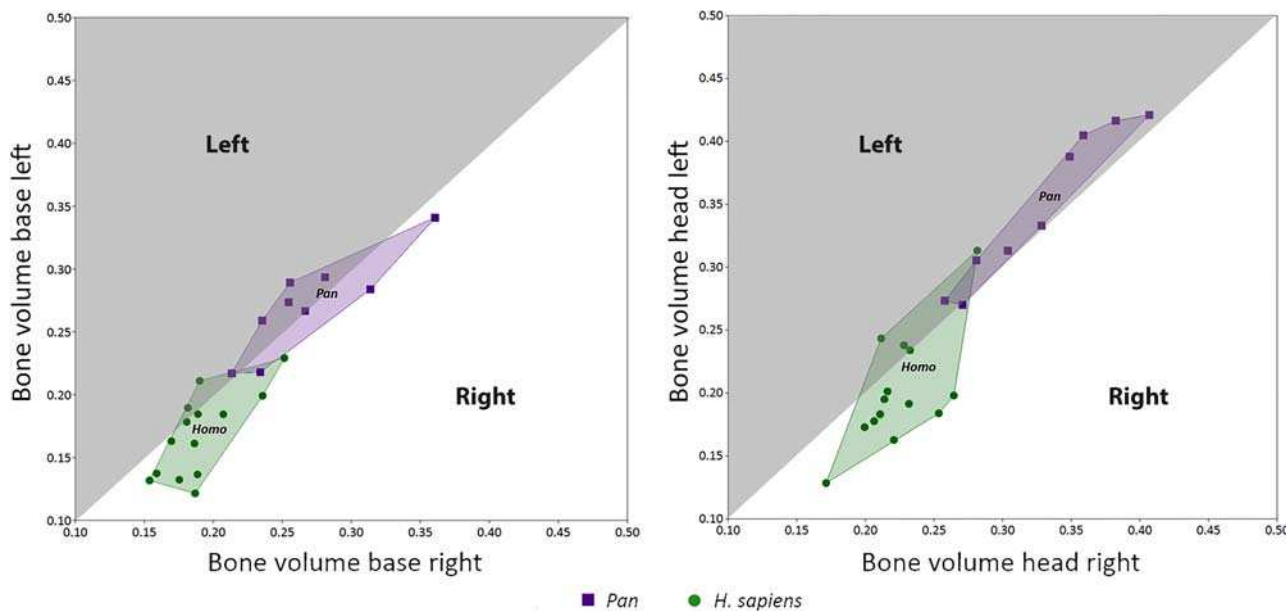


FIGURE 1 Bone volume of the first metacarpal base (left) and head (right) for both sides of each individual. Shaded area contains individuals demonstrating left directional asymmetry. *H. sapiens* (green dot) demonstrates a clear right directional asymmetry with relatively low BV/TV, while *Pan* (purple square) demonstrates a left directional asymmetry trend with relatively high BV/TV

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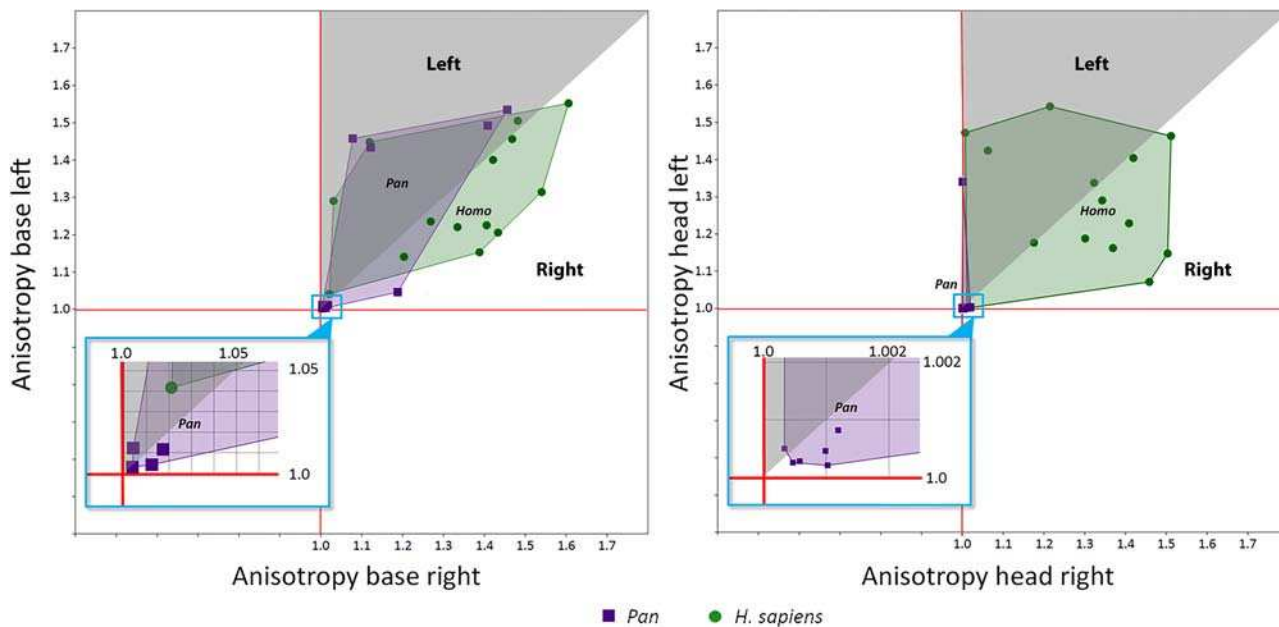


FIGURE 2 Degree of anisotropy of the first metacarpal base (left) and head (right) for both sides of each individual. The shaded area indicates individuals demonstrating a left directional asymmetry while the red line indicates isotropy. *H. sapiens* (green dot) variation in anisotropy for both regions, while *Pan* (purple square) is very constrained. The blue box is a magnified view of clustered individuals that approach total isotropy for both sides. This is particularly marked in the head of *Pan*, with six individuals contained between 1.0 and 1.002 on both sides

COLOR

284 biomechanical environment and, because of this; (2) the directional
 285 asymmetry of trabecular architectural variables (i.e., greater BV/TV,
 286 DA, and elastic modulus) in *H. sapiens* will be significantly greater on
 287 the right; (3) while *Pan* will exhibit no significant departure from a neu-
 288 tral (50%) distribution.

individuals from Syracuse (Sicily). The *Pan* cohort ($n = 9$ pairs) is com- 295
 posed of four wild-shot individuals from southern Cameroon (*Pan trog-* 296
lodytes spp.), three wild individuals from Côte d'Ivoire (*Pan troglodytes* 297
verus) and two wild-shot individuals from the Congo Basin (DRC) (*Pan* 298
paniscus). 299

289 **2 | MATERIALS AND METHODS**

290 **2.2 | Micro-CT scanning and tissue segmentation** 300

290 **2.1 | Study sample**

291 The *H. sapiens* Mc1 sample ($n = 14$ pairs) is composed of ten 1st–3rd
 292 century CE individuals from the Roman necropolis of Isola Sacra (Italy)
 293 (Prowse et al., 2008), two 19th century individuals from Tierra del
 294 Fuego (Chile/Argentina) (Marangoni et al., 2011), and two 20th century

The heads and bases of the paired Mc1 remains from Isola Sacra and 301
 Côte d'Ivoire were scanned without the metaphyses (as part of a previ- 302
 ous study) with a Skyscan (Aartselaar, Belgium) 1172 desktop Micro- 303
 CT scanner at an isotropic voxel resolution of 13.56 μm (parameters: 304
 100 kV, 0.094 mA, 0.5-mm aluminum filter, 0.25 rotation step, 360 305
 degrees of rotation, with two frame averaging). The remaining Mc1s 306

AQ6 **TABLE 2** Right/left count comparisons within and between groups

Variable	<i>Pan</i> ($n = 9$)			<i>Homo</i> ($n = 14$)			Between groups	
	R>L	DIRA, %	<i>B</i>	R>L	DIRA, %	<i>B</i>	χ^2	<i>p</i> Value
BV/TV head	1/9	-5.94	0.039	10/14	11.95	0.179	7.987	.005
BV/TV base	3/9	-1.38	0.508	12/14	12.64	0.013	6.626	.010
DA head	7/9	-2.93	0.180	9/14	1.01	0.424	0.471	.493
DA base	4/9	-5.80	1	10/14	2.57	0.180	1.675	.196
<i>E</i> head	2/9	-10.94	0.180	11/14	23.15	0.057	7.078	.008
<i>E</i> base	4/9	-2.54	1	12/14	22.32	0.013	4.407	.036

Abbreviations (BV/TV = bone volume; DA = degree of anisotropy; *E* = elastic modulus in gigapascals; R > L = # of individuals displaying right directional asymmetry; DIRA = average direction of asymmetry with negative numbers indicating a left directional asymmetry; *B* = *p* values for binomial exact test for deviations from an expected 50/50 distribution; χ^2 = *p* values for Pearson's χ^2 test to determine if directional asymmetry counts between groups are significantly different).

TABLE 3 Average absolute asymmetry within and between groups

Variable	Pan (n = 9) AA, %	Homo (n = 14) AA, %	Between groups	
			U	p Value
BV/TV head	5.99	16.21	20.00	.005
BV/TV base	6.44	14.74	34.00	.072
DA head	3.52	14.11	16.00	.002
DA base	8.95	9.95	50.00	.439
E head	11.84	29.82	27.00	.023
E base	11.14	26.24	34.00	.068

Abbreviations (BV/TV = bone volume; DA = degree of anisotropy; E = elastic modulus; AA = mean absolute asymmetry; U = Mann-Whitney U score; p = exact p value for Mann-Whitney U test).

were scanned in their entirety with a BIR ACTIS 225/300 high-resolution Micro-CT scanner at an isotropic voxel resolution ~30 μm (parameters: 130 kV and 100 IA using a 0.25 aluminum filter). The heads and bases of the complete Mc1 sample were isolated and cropped using Avizo 6.3 to allow for uniform comparison with those scanned without the metaphysis. Segmentation of bone tissue in each scan was accomplished using the Ray Casting Algorithm of Scher and Tilgner (2009).

2.3 | Trabecular bone analysis and visualization

Unless noted otherwise, all procedures were performed with medtool (Dr. Pahr Ingenieurs e.U.). After segmentation, trabecular and cortical bone were isolated using protocols outlined in Gross et al. (2014). In brief, opening-and-closing filters (kernel size = 3) were employed to remove natural cortical porosities, which permits creation of a smooth

shell that is then filled to create an inner- and outer-mask of the whole bone. The resultant cortical mask is then used to create an independent image of each tissue. This process is repeated, to replace the initial kernel size with one taking into account the average trabecular thickness measured by the BoneJ plugin (Doube et al., 2010) in ImageJ (Rasband, 1997; see also Gross et al., 2014).

We focus our analysis of asymmetry in trabecular structure on three variables: average bone volume to total volume fraction (BV/TV), degree of anisotropy (DA), and the elastic modulus (E), which is measured in gigapascals (GPa) (Pahr and Zysset, 2009). These variables were chosen because it has been demonstrated that body mass does not strongly correlate with BV/TV or DA (Barak, Lieberman, & Hublin, 2013; Doube, Klosowski, Wiktorowicz-Conroy, Hutchinson, & Shefelbine, 2011; Ryan & Shaw, 2013), and that they have a well-established correlation with mechanical loading and functional bone adaptation (Barak et al., 2011; Lambers, Bouman, Rinnac, & Hernandez, 2013; Odgaard, 1997; Pontzer et al., 2006; Uchiyama et al., 1999). Although the relationship between trabecular structure and E depends on the anatomical location and direction of loading (Morgan, Bayraktar, & Keaveny, 2003), it is an accepted proxy for bone strength (Helgason et al., 2008; Stauber et al., 2006). Herein we calculate E following the Zysset-Curnier model (Zysset, 2003) using a reference tissue value of E0 = 10 GPa; ν0 = 0.3; μ0 = 3 GPa, because it takes into account BV/TV and mean intercept length derived fabric, which has been demonstrated in several anatomical locations to be a better predictor of the mechanical properties of trabecular bone (~97%) than other models (Haïat et al., 2009; Maquer et al., 2015).

To analyze each variable throughout the epiphyseal head and base of each Mc1, a 5 mm spherical VOI was passed over a rectangular 2.5 mm 3D grid placed over the trabecular mask. From these VOIs, 350

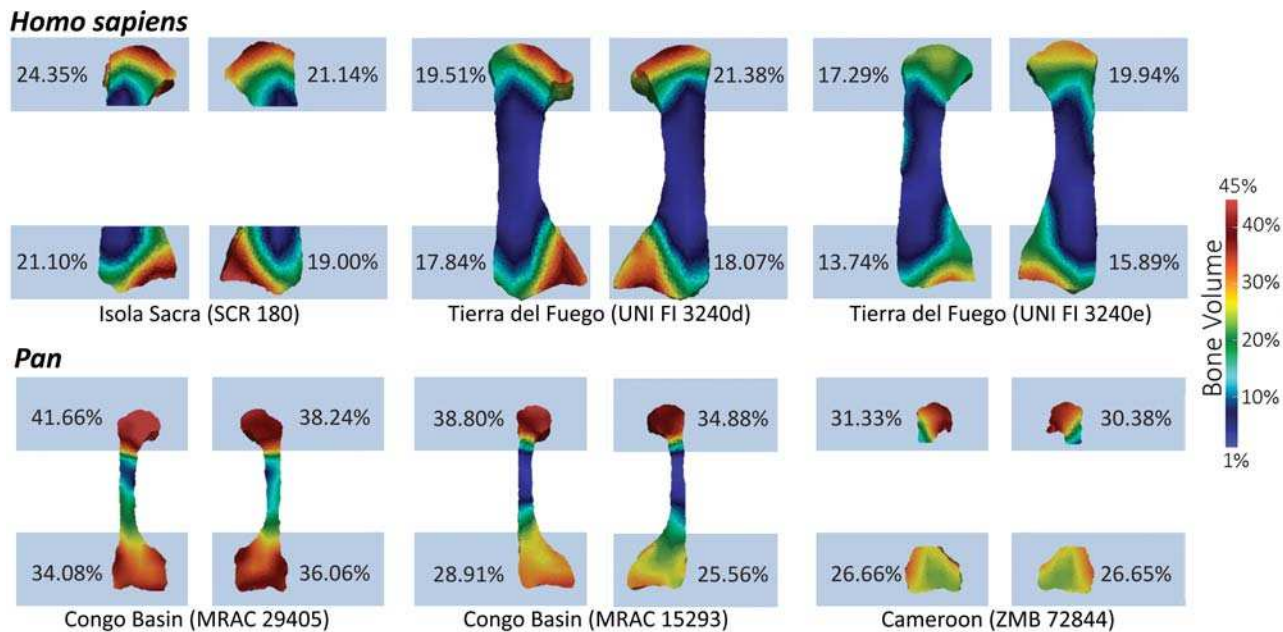


FIGURE 3 Mid-sagittal cross section of right and left first metacarpals exemplifying the site specific internal distribution and average bone volume for *H. sapiens* (top) and *Pan* (bottom). Average quantitative BV/TV (%) for the head and base are indicated in the shaded boxes

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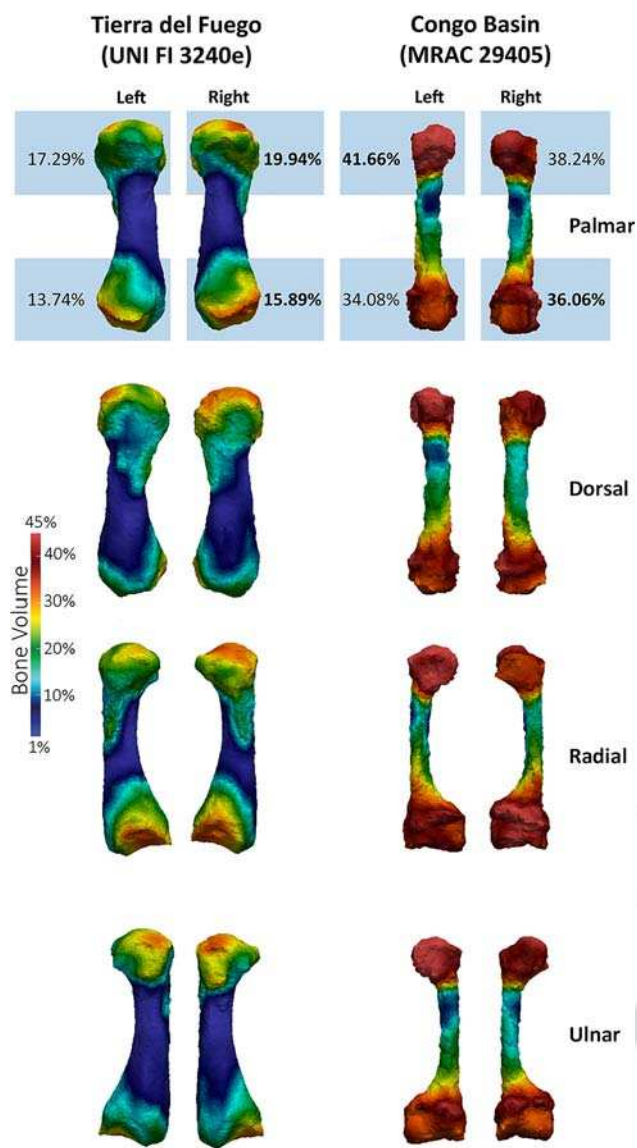


FIGURE 4 3D models showing the site specific BV/TV (%) distribution in the left and right first metacarpals in palmar, dorsal, radial, and ulnar views of a modern human (left) and a bonobo (right). Average quantitative BV/TV (%) for the head and base are indicated in palmar view with the greatest value from each side in bold

COLOR

100, where a positive number indicates right directional asymmetry (r) 363 and a negative number left directional asymmetry (l). Similarly, absolute 364 asymmetry (AA) is calculated by: $AA = |r - l| / ((r + l) / 2) \times 100$, with the 365 difference being a standardized measure of the magnitude of asymme- 366 try for comparison between groups (Palmer, 1994). Statistical analysis 367 of the resulting variables was performed using SPSS 20 (IBM), R ver- 368 sion 3.1.0, and PAST 3.04 (Hammer, Harper, & Ryan, 2001). Mann- 369 Whitney U tests were used to determine if the values for the left/right 370 variables differed significantly between Pan and Homo. Within-group 371 exact binomial tests were performed on DIRA counts to determine if 372 Pan and Homo departed from an expected 50/50 right- versus left- 373 distribution, while Pearson's χ^2 tests were performed to determine if 374 these counts differed significantly between the two groups. Mann- 375 Whitney U tests were performed to determine if absolute asymmetry 376 values differed significantly between the two groups. 377

3 | RESULTS 378

3.1 | Quantitative results 379

Averages and standard deviations for the mean (sides combined) and 380 side-specific (i.e., right and left) trabecular variables (BV/TV, DA, and E) 381 for the Pan and H. sapiens groups are shown in Table 1. On average, 382 Pan exhibits left directional asymmetry and H. sapiens exhibit a right- 383 directional asymmetry for each variable at the head and base. Mann- 384 Whitney U tests are significant between Pan and H. sapiens for all vari- 385 ables, with Pan being considerably more isotropic and having greater 386 overall BV/TV and E for both regions. It is also evident that Pan and H. 387 sapiens share a distinct difference in the pattern of trabecular variables 388 at the head and base, with the Mc1 head having greater BV/TV and E 389 but lower DA when compared with the base. Figures 1 and 2 present 390 bi-variate plots of BV/TV and DA distribution in each epiphysis. As 391 noted above, Pan has greater BV/TV in both the head and base and a 392 greater number of individuals that exhibit a left directional asymmetry 393 (see below). Although there is overlap between the two groups in DA 394 values at the Mc1 base, the majority of Pan individuals approach iso- 395 tropy (DA close to 1) on both sides at the head. 396

Table 2 presents the results of DIRA and right directional asymme- 397 try individual counts, along with results from the within-group binomial 398 exact and between-group χ^2 tests. The binomial exact tests found that 399 the right directional asymmetry for H. sapiens is significant at the Mc1 400 base for BV/TV and E, while the left directional asymmetry for Pan is 401 significant at the head for BV/TV. The between groups χ^2 tests found 402 that the right directional asymmetry count distribution was significantly 403 different from the expected 50/50 right versus left distribution for 404 BV/TV and E for both the Mc1 head and base. These differences in 405 frequency can also be seen in Figures 1 and 2 for BV/TV and DA, 406 respectively. 407

Table 3 presents the results of Mann-Whitney U tests for signifi- 408 cant differences in absolute asymmetry between H. sapiens and Pan. 409 BV/TV, DA, and E all exhibit significantly greater absolute asymmetry 410 at the Mc1 head, but not at the base. 411

351 average values for each trabecular variable (BV/TV, DA, and E) within 352 each epiphyseal segment were computed. To visualize and qualitatively 353 compare the site-specific distribution of BV/TV, we first created a 3D tet- 354 rahedron mesh of the trabecular mask using HyperMesh® (Altair Engineer- 355 ing, Inc., USA), onto which we then mapped the BV/TV results from each 356 VOI of the background grid analysis. These results were uniformly scaled 357 between 1% and 45% and visualized using Paraview (v. 3.14.1, paraview. 358 org), which allows the color-coded models of BV/TV to be viewed as com- 359 plete trabecular mesh or by a user-defined 2D cross section.

2.4 | Calculation of asymmetry 360

361 Calculation of asymmetry follows the handedness index of Mays 362 (2002) for directional asymmetry (DIRA): $DIRA = (r - l) / ((r + l) / 2) \times$

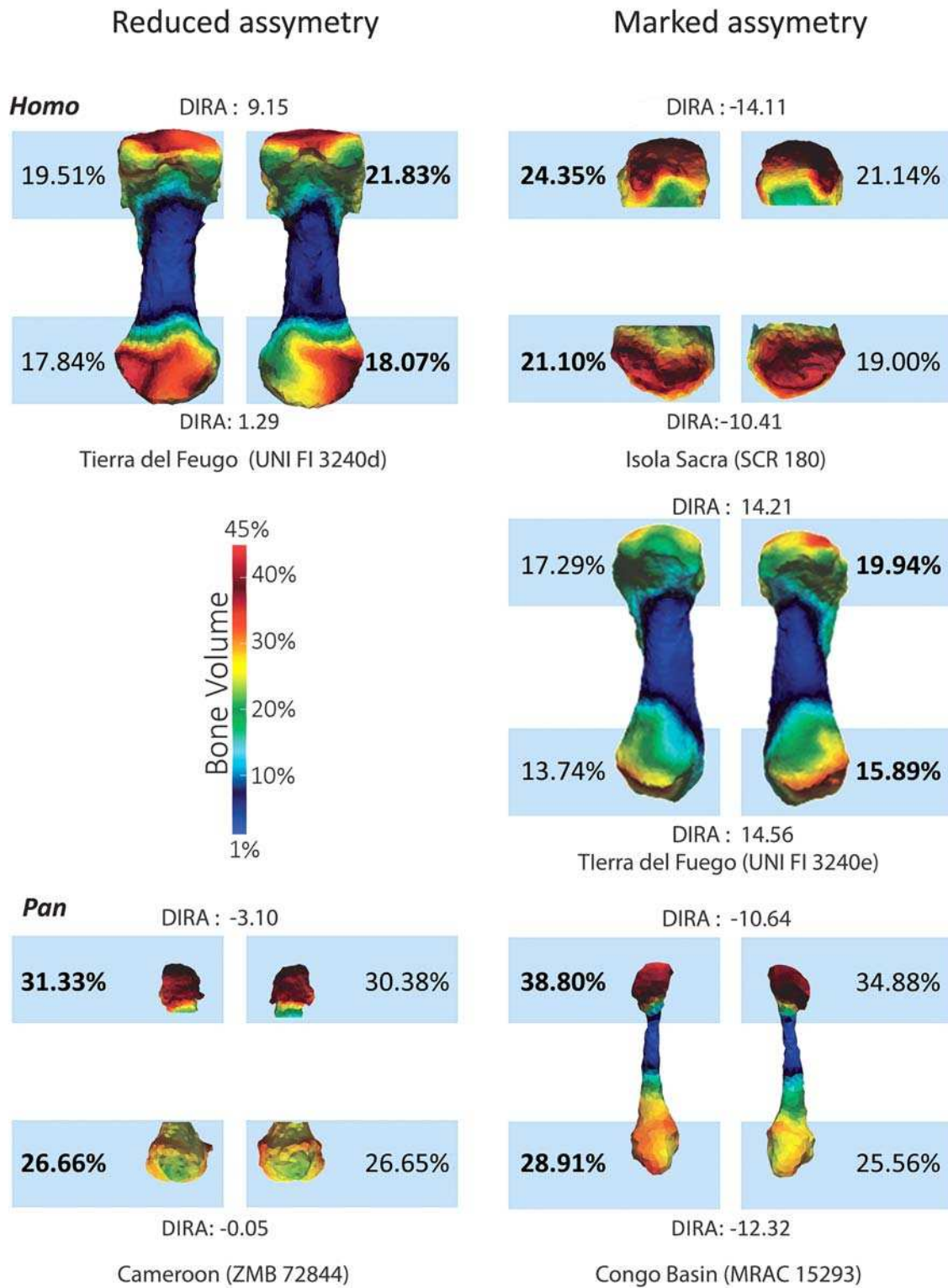


FIGURE 5 Representative 3D models of right and left first metacarpals BV/TV (%) and levels of directional asymmetry (DIRA). The greater average BV/TV for the region indicated by the shaded boxes are in bold. Individuals with a left directional asymmetry are indicated by a negative number, while those with right directional asymmetry are indicated by a positive number

3.2 | Qualitative results

Figure 3 is a mid-sagittal cross section exemplifying the site-specific internal bone volume distribution and individual quantitative averages

at the Mc1 head and base for a selection of *H. sapiens* and *Pan* while Figure 4 is an external view (i.e., complete trabecular mesh). The differences in site-specific bone volume concentration and distribution are reflected in the color maps, and illustrate that the *Pan* sample is more

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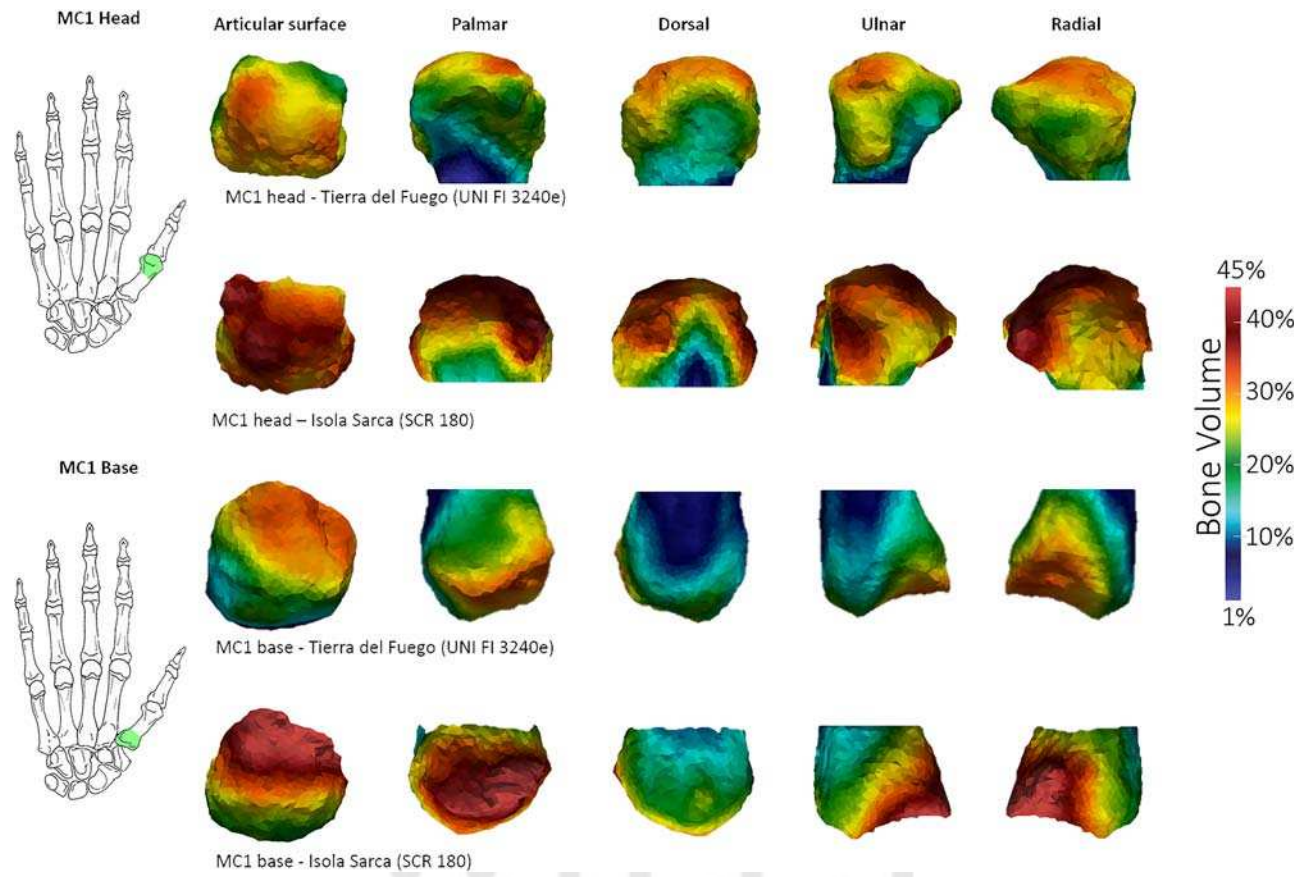


FIGURE 6 Example of site specific bone volume distribution in the first metacarpal head (top two rows) and base (bottom two rows) for two *H. sapiens* individuals (SCR 180 and UNI FI 3240e)

COLOR

419 uniform internally in both Mc1 regions, while concentrations in the *H.*
 420 sapiens are found towards the articular surface areas. Also of note are
 421 the variations in distribution between left and right sides, with a greater
 422 radial concentration at the right base and head in the individual from
 423 Tierra del Fuego (UNI FI 3240e, Figures 3 and 4).

F5 424 Figure 5 shows examples of low and marked directional asymme-
 425 try for representative *H. sapiens* and Pan. Herein the complexity of
 426 determining asymmetry is made clear because although the bone vol-
 427 ume quantitative averages provide evidence for a right or left direc-
 428 tional asymmetry, the concentrations and uniformity do vary between
 429 the head and base regions (e.g., MRAC 15293 compared with ZMB
 430 72844). Furthermore, site-specific distribution and concentration of
 431 bone volume also varies between individuals (UNI FI 3240d base, see
 432 also cross section in Figure 3). For example, in certain Pan (MRAC
 433 29045) individuals the right/left directional asymmetry is unclear, with
 434 the head being greater on the right directional but greater on the left
 435 at the base or vice versa.

F6 436 Figure 6 shows the right Mc1 head and base for two *H. sapiens*
 437 individuals (UNI FI 3240e and SCR 180) in standard anatomical views.
 438 Even with different average values for each individual, the site-specific
 439 BV/TV pattern in *H. sapiens* shows that the trabecular distribution at
 440 the head is fairly concentrated at the articular surface, with the great-
 441 est volumes found at the contact areas for the first proximal phalanx.
 442 This is also the case at the base, but the highest concentrations are

found at the palmar aspect of the articular surface and extend distally 443
444

Figure 7 shows the site-specific bone volume distribution for the 445
right Mc1 head and base for two Pan individuals (MRAC 29045 and 446
ZMB 72844) from standard anatomical views. The cause for the much 447
higher average quantitative BV/TV is evident here, as the trabeculae 448
are much more evenly distributed and palmarly concentrated through- 449
out the head. This is not as marked at the base where the greatest con- 450
centrations are not actually at the articular surface, but are instead 451
slightly distal to the surface on the dorsal, ulnar, and radial sides, which 452
contrasts with the pattern found at the *H. sapiens* Mc1 head and base 453
(Figure 6). 454

4 | DISCUSSION 455

We sought to test whether skeletal asymmetries in trabecular bone 456
were consistent with the assumption of increased mechanical loading 457
on the dominant limb, following the mechanostat model of bone func- 458
tional adaptation (Frost, 1987). Overall we found that the right direc- 459
tional asymmetry in measured epiphyseal trabecular variables of the 460
paired first metacarpals (Mc1) from *H. sapiens* matched expectations, 461
while the left directional asymmetry of Pan countered our expecta- 462
tions. We also report that, compared with Pan, *H. sapiens* have signifi- 463
cantly lower bone volume (BV/TV) and elastic modulus (*E*), but higher 464

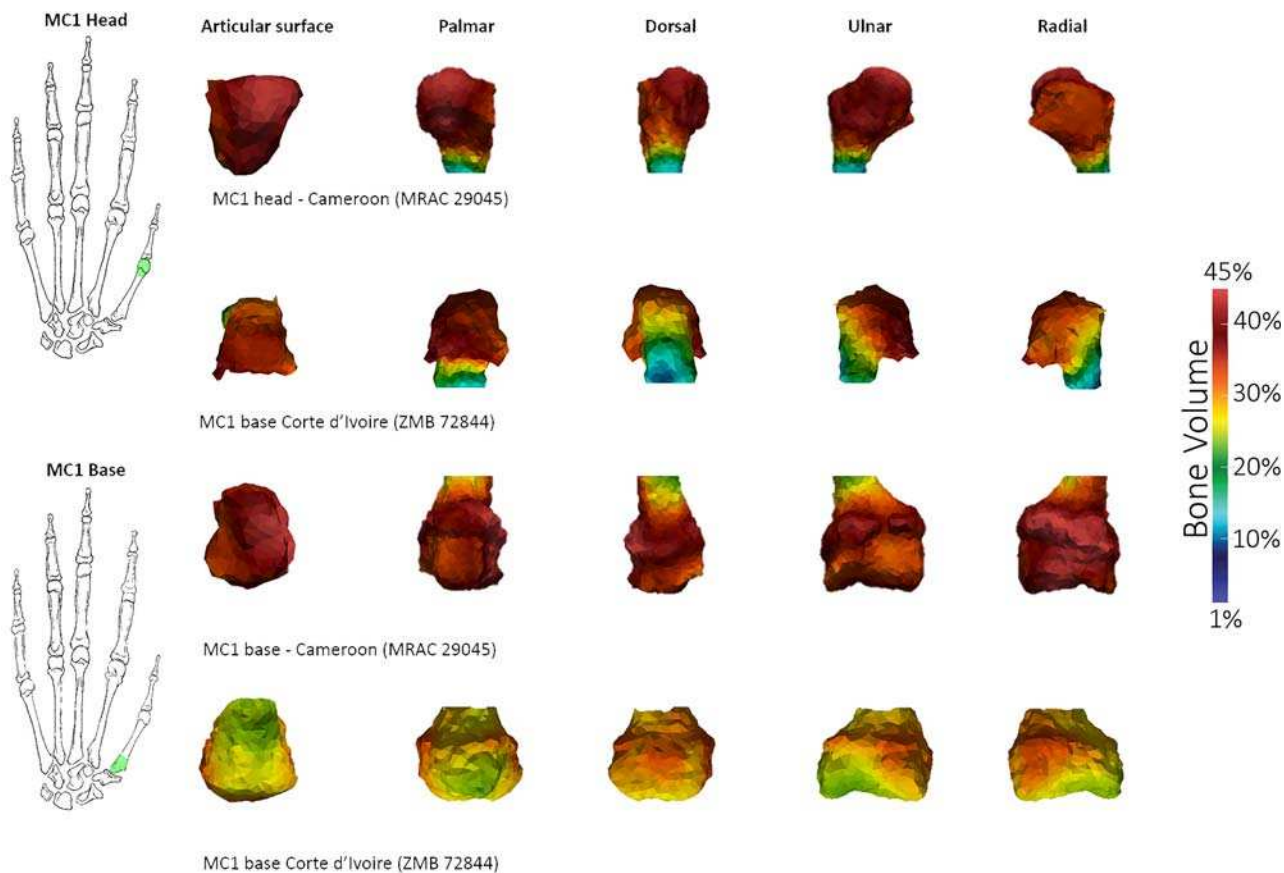


FIGURE 7 Example of site specific bone volume distribution in the first metacarpal head (top two rows) and base (bottom two rows) for two *Pan* Individuals (MRAC 29045 and ZMB 72844)

COLOR

465 degree of anisotropy (DA) in both regions. There is also a consistent
466 head/base pattern evident in *H. sapiens* and *Pan*, with higher DA but
467 lower BV/TV and *E* at the Mc1 base compared with the head. The indi-
468 vidual site-specific BV/TV distribution models make it clear that many
469 of the quantitative results are explained by the individual variation in
470 the distribution of trabeculae, and suggest that the relationship
471 between hand preference and directional asymmetry in the Mc1 epi-
472 physeal trabecular architecture is not as straightforward as initially
473 hypothesized.

474 4.1 | Directional asymmetry in *Homo sapiens*

475 In counts of right or left directional asymmetry we found a significant
476 right directional asymmetry in BV/TV and *E* in the *H. sapiens* Mc1
477 base, while the *Pan* Mc1 reached a significant left directional asymme-
478 try for BV/TV at the head. Comparisons between the two groups
479 revealed that the counts reached significance for bone volume in both
480 regions and elastic modulus at the base. Finally, *H. sapiens* displayed
481 greater levels of absolute asymmetry for all trabecular variables in both
482 regions with significant differences between the two groups existing at
483 the Mc1 head.

484 We consider statistically significant greater trabecular variables
485 (BV/TV and *E*) in the Mc1 base as the best indicator of loading related
486 to hand preference. This appears to be supported by the palmar and

radial bone volume concentrations at the articular surface, which con- 487
form with areas of localized remodeling in response to mechanical 488
stimuli (Christen et al., 2014; Cresswell et al., 2016; Schulte et al., 489
2013) and speak to loading during flexion and forceful opposition 490
(Ladd et al., 2014). These results join those of Lazenby, Angus, Cooper, 491
and Hallgrímsson (2008) and Lazenby, Cooper, et al. (2008), who exam- 492
ined the directional asymmetry in paired second metacarpals and found 493
a significant right directional asymmetry for trabecular bone volume at 494
the head, mid-shaft cross-sectional geometry of the cortex, and medio- 495
lateral articular dimensions. 496

497 4.2 | Directional asymmetry in *Pan*

498 We predicted that there would be no directional asymmetry detected 498
in the *Pan* Mc1s because the thumb is removed from loading during 499
lateralized terrestrial locomotion (Arcadi & Wallauer, 2011) and that 500
other potential behaviors that produce asymmetrical loading of the 501
thumb (e.g., arboreal locomotion, tool use) would not be detected at a 502
group level. Our results did not support this prediction and instead we 503
found a left directional asymmetry trend in the *Pan* Mc1. This result is 504
not consistent with previous studies of *Pan* trabecular bone (Lazenby 505
et al., 2011) that did not find any directional asymmetry. If the left 506
directional asymmetry found in this study is a byproduct of manipula- 507
tion, it is inconsistent with wild observational data that indicate only 508

AQ2

509 individual-level, but not group-level, hand preference (Boesch, 1991;
 510 Marchant & McGrew, 2007; McGrew & Marchant, 1992, 1997).
 511 Although the mechanostat model is admittedly oversimplified, it seems
 512 unlikely that variation in hormonal, genetic, and cellular responses
 513 across different anatomical regions could explain differences in right/
 514 left directional asymmetry within a single skeletal element. However,
 515 future studies could address this question, such as in a mouse model
 516 after Wallace et al. (2015), where right/left loading is controlled for as
 517 opposed to fore/hind limb.

518 We do, however, find a similar pattern to that reported here des-
 519 cribed in a cortical bone assessment of Sarringhaus, Stock, Marchant,
 520 and McGrew (2005) who found a left directional asymmetry in the
 521 humeri and right directional asymmetry in the second metacarpals of
 522 *P. troglodytes*. They discussed a tradeoff in loading environments
 523 based on observations of wild chimpanzees (Hunt, 1991), where pref-
 524 erence for manual support of the left-hand leaves the right free to col-
 525 lect food (Sarringhaus et al., 2005). Such a preference is noted in
 526 captive groups, with a left-hand preference existing for hanging (Mor-
 527 cillo, Fernandez-Carriba, & Loeches, 2006) and during front-forward
 528 descent, where the palm makes direct contact with the substrate (Hop-
 529 kins, 2008). These observations are paired with studies of chimpanzee
 530 soft tissue anatomy that have found greater muscle mass on the left
 531 upper limb and greater muscle moment arms on the right (Carlson,
 532 2006). These studies suggest that there may be greater asymmetry in
 533 Pan upper limb use and loading than previously thought, which could
 534 override signals of hand preference during manipulation and complicate
 535 direct comparisons between Pan and *H. sapiens*. Clarification of this
 536 issue requires the incorporation of more than a single skeletal element
 537 or osseous tissue. In the absence of such a comparison in the current
 538 study, we suggest that the homogenous distribution of bone volume,
 539 high elastic modulus, and near total isotropy in the Pan Mc1 is better
 540 explained by lateralized loading during locomotion and postural sup-
 541 port. Given our finding of overall less absolute asymmetry in the Pan
 542 Mc1 in relation to that of *H. sapiens*, this type of lateralized loading
 543 appears more balanced, but implies that questions pertaining to skilled
 544 tool use and hand preference may only be appropriate for committed
 545 terrestrial bipeds.

546 4.3 | Mc1 loading in *Homo sapiens*

547 Compared with other primates, the low BV/TV of *H. sapiens* reported
 548 here agrees with reports of less dense trabecular architecture in
 549 humans in other skeletal elements (Chirchir et al., 2015; Griffin et al.,
 550 2010; Maga et al., 2006; Ryan & Shaw, 2012, 2013, 2015), including
 551 the hand (Schilling et al., 2013; Tsegai et al., 2013). The thumb has
 552 been described as operating as a single functional unit during flexion
 553 (Ladd et al., 2014), such that the three phalanges, trapezium, and sup-
 554 porting thenar musculotendon network act in concert to rotate and
 555 support the distal pad during the forceful opposition of the other fin-
 556 gers and/or manipulated objects (Brand & Hollister, 1993; Diogo et al.,
 557 2012; Landsmeer, 1955; Li & Tang, 2007; Marzke et al., 1999). Our
 558 finding of greater BV/TV and *E* at the head relative to the base sug-
 559 gests that the Mc1 head experiences greater loading, but this may also

be a result of loads being transferred into the broad surface of the tra-
 pezium (Marzke, 2013). Visually, the site-specific BV/TV concentra-
 tions at the articular surface of the head and palmar-radial
 concentration at the base are consistent with loads incurred while
 using a flexed and abducted thumb (e.g., key/pinch/power grips),
 where the base of the first metacarpal translates ulnarly and the radial
 articular surface resists the load (Halilaj et al., 2014). Such an interpre-
 tation also appears consistent with clinical micro-CT trabecular studies,
 which report a mirrored palmar-ulnar concentration in the trapezium
 that is thought to be an indication of remodeling in response to
 axial displacement of force during thumb loading (Ladd et al., 2014;
 Lee et al., 2013; Nufer et al., 2008). As such, this pattern appears to be
 biomechanically consistent between bones, but would benefit by hav-
 ing a broader comparison of trabecular structure across the remaining
 bones of the hand.

575 4.4 | Mc1 loading in *Pan*

576 We find that the high BV/TV, low DA, and head/base pattern reported
 577 for Pan Mc1s here agrees with results derived from a similar Mc1 sam-
 578 ple using single VOIs by Lazenby et al. (2011). A strict interpretation of
 579 the mechanostat model would suggest that the extremely high BV/TV
 580 and *E* in the Pan Mc1, when compared with *H. sapiens*, is a direct result
 581 of high impact mechanical loading. This pattern would be consistent
 582 with the scenario described above, where the high BV/TV and *E* in the
 583 Pan Mc1 compensate for the reduced thenar musculature (Diogo et al.,
 584 2012; Marzke et al., 1999) and smaller joint surfaces in the thumb com-
 585 plex (Marzke, 2013) during locomotion and postural support. However,
 586 as discussed above, bone functional adaptation is a complex aspect of
 587 biology and our results are not inconsistent with a view that systemic
 588 differences in hormones, genes (Patemoster et al., 2013; Wallace et al.,
 589 2010; Yerges et al., 2010), and cellular response to loading (Wallace
 590 et al., 2015) may also work to explain the genera-level differences
 591 reported here. This being the case, a one-to-one correlation between
 592 loading and bone morphology is not supported by our results and, we
 593 can only suggest that the greater BV/TV and *E* in the Pan Mc1 are
 594 byproducts of systemic hormonal/genetic differences in combination
 595 with loading.

596 Even so, evidence for localized loading and bone remodeling does
 597 exist in the site-specific areas of high BV/TV concentration in the Pan
 598 Mc1 base, visible just above the articular surface. These regions appear
 599 correspondent with the muscle attachment sites responsible for flexion
 600 of the thumb (Diogo, Potau, & Pastor, 2013; Marzke et al., 1999). This
 601 is intriguing in light of the report of Marzke et al. (2015), who recog-
 602 nized previously unobserved hand grips during food processing that
 603 appear to involve forceful loading of the thumb. These include a thrust-
 604 ing movement involving large fruits held in the pocket between the
 605 thumb and index, and a variation of the transverse hook grip that
 606 depends on leverage provided by the thumb to strip away meat
 607 clenched between teeth. Although this result suggests that the rela-
 608 tionship between muscle attachment sites and trabecular response
 609 requires additional exploration, the uniformity of bone volume,
 610 extremely low anisotropy, and high elastic modulus speaks to a greater

611 demand for multi-axial loading than manipulation or feeding alone.
612 Being that these grips are also observed during arboreal locomotion,
613 which is very complex and variable throughout life (Sarringhaus et al.,
614 2014), our results are perhaps best explained by loading during contact
615 with a highly variable substrate. If this interpretation is correct, then it
616 implies that the signal from subtler loading scenarios, such as those
617 during manipulation, may be reduced or lost in favor of loading regimes
618 with higher peak loading.

619 5 | CONCLUSION

620 In summary, we found that the first metacarpal trabecular pattern
621 and distribution were consistent with the biomechanical role of the
622 thumb and found that counts of right directional asymmetry for
623 average bone volume and elastic modulus at the base reached sig-
624 nificance, which appears to be concordant with the 85–95% right-
625 hand preference reported cross-culturally. Contrary to our expecta-
626 tions we also found a significant left directional asymmetry at the
627 Pan Mc1 head for bone volume that, combined with the finding of
628 extremely low DA and high E in both head/base regions, is best
629 explained as a reflection of individual preference for left side later-
630 alized loading during locomotion and postural support. We also
631 report greater BV/TV and E in the Pan Mc1, when compared with
632 *H. sapiens*, which we stress is likely a reflection of a systemic hor-
633 monal/genetic difference between the two groups and is likely not
634 an indication of greater loading in the Pan thumb. This is an impor-
635 tant consideration that should be kept in mind during the analysis
636 and interpretation of hominin fossil remains (see discussion in Wal-
637 lace et al., 2015). As such, we suggest that behavioral studies con-
638 cerned with the manifestations of bone functional adaptation
639 should adopt a layered analysis that incorporates multiple techni-
640 ques to check the biomechanical agreement of various osseous tis-
641 sues and taxa.

642 To conclude, we found directional asymmetry in the first metacar-
643 pal trabecular architecture, but caution that the cause of this bias is not
644 always a clear indication of individual hand preference during manipula-
645 tive tasks and suggest that additional analyses be applied to multiple
646 skeletal elements and other osteological features (e.g., cortical bone)
647 whenever possible. We also found that our interpretation of the quan-
648 titative results and potential loading histories were greatly aided by
649 referring to the site-specific bone volume distribution models. As such,
650 our analysis builds upon previous studies that have used trabecular
651 architecture to investigate loading history and its relationship to bone
652 functional adaptation. We conclude the characterization and visualiza-
653 tion of trabecular architecture is a method that should be joined with
654 previously established techniques to supplement fossil studies con-
655 cerned with the evolution of handedness. Such an application has great
656 potential to provide missing information prior to the advent of stone
657 tool manufacture, and would thus improve our understanding of the
658 hypothesized cause and effect relationship between knapping, brains,
659 and behavior.

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