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Craniofacial skeletal response to encephalization: How do we know what we think we know?

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Abstract

Dramatic changes in cranial capacity have characterized human evolution. Important evolutionary hypotheses, such as the spatial packing hypothesis, assert that increases in relative brain size (encephalization) have caused alterations to the modern human skull, resulting in a suite of traits unique among extant primates, including a domed cranial vault, highly flexed cranial base, and retracted facial skeleton. Most prior studies have used fossil or comparative primate data to establish correlations between brain size and cranial form, but the mechanistic basis for how changes in brain size impact the overall shape of the skull resulting in these cranial traits remains obscure and has only rarely been investigated critically. We argue that understanding how changes in human skull morphology could have resulted from increased encephalization requires the direct testing of hypotheses relating to interaction of embryonic development of the bones of the skull and the brain. Fossil and comparative primate data have thoroughly described the patterns of association between brain size and skull morphology. Here we suggest complementing such existing datasets with experiments focused on mechanisms responsible for producing the observed patterns to more thoroughly understand the role of encephalization in shaping the modern human skull.

KEYWORDS

brain, cranial capacity, development, human evolution, mouse models, skull morphology

1 | INTRODUCTION

The human head is unique among mammals. The distinctive morphology and evolution of the human skull is hypothesized to have been influenced by:

1. *Selective pressures* in response to biomechanical forces and energetic requirements related to mastication and respiration (e.g., Bastir & Rosas, 2013; Holton, Yokley, Froehle, & Southard, 2014; Lieberman, 2008, 2011; Rosas & Bastir, 2002; Yokley, Holton, Franciscus, & Churchill, 2009); and
2. *Development shifts* in brain ontogeny and embryonic brain-skull interactions that led to large-scale shifts in the size and position of the different cranial skeletal modules (e.g., Bastir et al., 2010; Bruner, 2004, 2007; Lieberman, 2011; Lieberman, Krovitz, & McBratney-Owen, 2004; Lieberman, McBratney, & Krovitz, 2002; Martínez-Abadías, Esparza, et al., 2012; Weidenreich, 1941).

Biomechanical forces related to mastication and respiration are generally thought to significantly impact the oral, nasal, and pharyngeal cavities and ultimately the facial skeleton, while changes in brain growth and size are considered to have more generalized, profound effects on all regions of the skull (Bastir & Rosas, 2016; Lieberman, 2011; Moss & Young, 1960). However, acknowledging the significant influence of the growing brain on skull morphology does not provide a mechanistic explanation for *how* the skull changed ontogenetically or over evolutionary time in response to increases in brain size.

Increased brain size is a critical feature of human evolution. Estimates of hominin cranial capacities, commonly used as a proxy for brain size, range from a diminutive 375 cc for *Australopithecus afarensis* (Holloway, 1995) to the current worldwide average of 1,350 cc in modern humans (Beals et al., 1984; Lieberman, 2011): a 3.6 fold increase. Relative to brain size, body size does not appear to have changed as drastically over the course of hominin evolution. Rather, current data point away from a gradual increase and toward species-specific trends in body mass, with *Au. afarensis* and *H. erectus* being relatively large-bodied, while *Au. africanus*, *H. habilis*, and *H. floresiensis* tended to have smaller bodies (Grabowski, Hatala, Jungers, & Richmond, 2015). Varying degrees of sexual dimorphism in body size also contribute

to variation in fossil body size estimates (McHenry, 1992). However, even using the smallest estimation of body size for *Au. afarensis*, there has only been an approximately 2-fold increase in body size for modern humans (Grabowski et al., 2015; Ruff, Trinkaus, & Holliday, 1997). These differential increases in brain and body size signal *encephalization*: an evolutionary increase in the size of the brain relative to an organism's total body mass. Encephalization results in a contemporary human brain size that exceeds the anthropoid primate expectation by approximately 3–4 times (Halley & Deacon, 2017) and is a hallmark of hominin evolution (Jerison, 1979; Lieberman, 2011; Rightmire, 2004).

Along with the dramatic increase in absolute and relative brain size throughout hominin evolution, the human skull has acquired a suite of cranial traits that is unique among extant primates, including a domed cranial vault, highly flexed cranial base, and retracted facial skeleton. Indeed, this suite of traits is believed to be a direct result of encephalization along the hominin lineage (Bastir, Rosas, Stringer, et al., 2010; Bruner, 2007; Hallgrímsson & Lieberman, 2008; Lieberman, 2008; Neubauer, Gunz, & Hublin, 2010). Fossil evidence and comparative primate studies provide strong links between the radical increase in relative brain size during hominin evolution and changes in skull morphology (Bastir, Rosas, Stringer, et al., 2010; Ross & Henneberg, 1995; Ross & Ravosa, 1993; Spoor, 1997). Countless genetic and environmental factors contribute to skull growth; however, brain growth appears to be the primary biomechanical driver of this process, one with the potential to cause biochemical changes that affect molecular and cellular dynamics. While we know that extracellular molecules and mechanical stimuli contribute to the differentiation of mesenchymal progenitors into osteochondro progenitor cells that will form the bones of the skull (Ikegame et al., 2001; Long, 2012; Palomares et al., 2009; Plotkin & Bivi, 2014; Robling, Fuchs, & Burr, 2014; Sato et al., 1999), the mechanistic interactions between the skull and brain, which produces mechanical forces that contribute to these chemical signals, are not well understood.

Here we review the evidence for human encephalization and the current understanding of the association between increased brain size and changes in skull morphology evident in the hominin fossil record and across comparative primate data sets. We present a summary of the embryogenesis of the brain and skull to demonstrate how their development is linked and provide a foundation for understanding the importance of early development in producing the human brain and skull phenotypes. Finally, we stress that the biological basis of evolutionary modifications of the craniofacial skeleton related to encephalization requires investigation beyond comparative primate analyses and the fossil record. We provide suggestions for how hypotheses about proposed mechanisms underlying the complex relationship between the soft and hard tissues of the human head can be tested.

2 | HUMAN ENCEPHALIZATION

Neurologists and paleoneurologists have studied the morphological and architectural evolution of the human brain by examining salient changes and proposing hypotheses pertaining to overall brain morphology, relative size of different neural structures, and modifications to neural composition (e.g., Bruner, 2004; Bruner, Manzi, & Arsuaga, 2003; Falk et al., 2000; Fjell et al., 2013; Geschwind & Rakic, 2013; Holloway, 1995; Holloway, Broadfield, Yuan, Schwartz, & Tattersall, 2004; Holloway & De La Costelareymondie, 1982; Rakic, 1995; Teffer et al., 2013; Teffer & Semendeferi, 2012). Yet, without fossil brains to study, the nature of these changes and their impact is difficult to gauge. However, paleoneurologists and paleoanthropologists have found a way to quantify a significant attribute of hominin fossil brains: brain size. Through the use of endocasts—natural, man-made, or digital representations of the interior of the neurocranium—cranial capacities can be measured, and brain sizes of fossil hominins quantified (de Sousa & Wood, 2007; Falk, 1987; Holloway et al., 2004; Neubauer & Hublin, 2012).

Increases in brain size, especially of the cerebral cortex, the largest and most complex component of the mammalian brain, is evident across the evolution of vertebrates. Humans, nonhuman primates, cetaceans, and elephants all show tremendous increases in brain size across evolutionary time scales (O'Leary, Chou, & Sahara, 2007). However, when controlling for body size, the human brain is extreme among primates. Strepsirrhines have brains that are approximately twice as large as similarly-sized rodents, anthropoid primates have brains that are additionally twice as large as similarly-sized strepsirrhines, and human brains are three to four times larger than expected for a similarly-sized anthropoid primate (Halley & Deacon, 2017).

Brain sizes of fossil hominins have traditionally been estimated through the use of cranial capacities or endocranial volumes (e.g., Falk, 1987; Holloway et al., 2004; Ruff et al., 1997; Zollikofer & Ponce de León, 2013) (Figure 1), recognizing that such estimates cannot accurately account for variation in the relative contributions of neural tissue, meninges, and cerebrospinal fluid (Bruner, 2004; de Sousa & Wood, 2007; Falk, 1987; Neubauer, 2015). Autopsies of modern human females and males provide average brain size estimates of approximately 1,290 and 1,450 cm^3, respectively (de Sousa & Cunha, 2012; Dekaban & Sadowsky, 1978). Paleoanthropological studies recognize that sexual dimorphism and the inability to accurately sex fossil specimens may contribute to variation in the estimates of cranial capacity (de Sousa & Cunha, 2012; de Sousa & Wood, 2007; Rightmire, 2004).

Absolute brain size has been utilized as a criterion for the inclusion of fossil specimens within the genus *Homo* and the splitting of hominin ancestral species (Leakey, Tobias, & Napier, 1964; Wood, 1992; Wood & Collard, 1999); however, absolute brain size is rarely used as a correlate of biological significance based upon Jerison's arguments regarding brain–body allometry (Jerison, 1977, 1979). Instead, measures of *relative* brain size are used. To account for brain–body scaling expectations, Jerison defined encephalization as the size of the brain relative to body size (Jerison, 1977, 1979; Ruff et al., 1997), with fossil hominin body sizes being derived from estimates of body mass that utilize the femur, pelvis, vertebral bodies, or even cranial measurements (Rightmire, 2004; Ruff et al., 1997). While some scholars continue to explore the importance of absolute brain size or neural complexity as significant influences in human evolution (Deaner, Isler, Burkart, & van Schaik, 2007; Kaas, 2000; Marino, 2006; Roth & Dicke, 2005), the bulk of modern hominin evolutionary studies, and this review, adopt Jerison's (1977, 1979) definition of encephalization and relative brain size.

Jerison's (1979) work produced a reliable way to quantify encephalization: the encephalization quotient (EQ), based upon the scaled relationship between brain and body mass estimated across mammalian taxa:

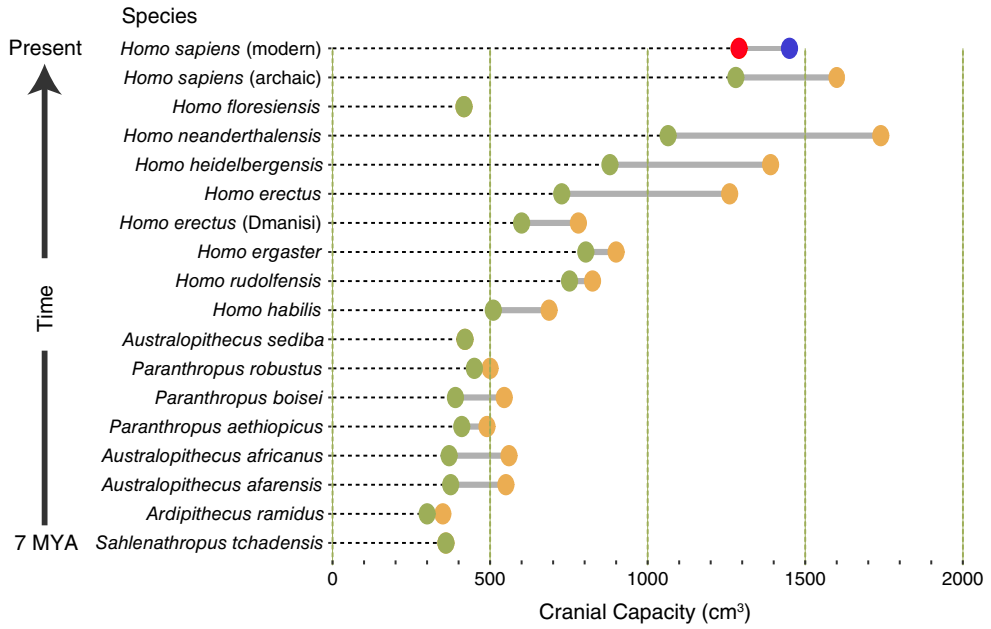

FIGURE 1 Estimated cranial capacity across hominin species ordered by their estimated geological age. Red and blue circles: Average cranial capacity for female and male, respectively, modern *Homo sapiens*. Green and yellow circles: Minimum and maximum cranial capacity estimates for fossil hominins. Species showing only a green circle indicate that only a single cranial capacity estimate was available in the literature (de Sousa & Cunha, 2012; Elton, Bishop, & Wood, 2001; Holloway et al., 2004; Rightmire, 2004)

$$EQ^1 = \text{estimated brain weight} / \left(0.12 \times \text{estimated body weight}^{2/3}\right)$$

This formulation was challenged by Martin (1981), who investigated an extended number of placental mammals that provided a broader data set of both brain and body size. Martin (1981) proposed a revised equation:

$$EQ^2 = \text{brain mass} / \left(11.22 \times \text{body mass}^{0.76}\right)$$

that many recent studies have adopted (de Sousa & Cunha, 2012; Holloway et al., 2004; Ruff et al., 1997).

Paleoanthropology has produced a robust record from which the pattern of encephalization can be traced from fossil hominins to modern humans. Depending on methodologies used, the average body size is estimated at 38–39 kg for *Australopithecus afarensis* and 46–64 kg for modern *Homo sapiens* (de Sousa & Cunha, 2012; Grabowski et al., 2015; Ruff et al., 1997). Brain size has increased from an estimated 375 cc for *Au. afarensis* to approximately 1,350 cc for modern *Homo sapiens* (Beals et al., 1984; Holloway, 1995; Holloway et al., 2004; Lieberman, 2011). These differential increases in brain size versus body size in the 3.5 million years leading to modern humans has resulted in an EQ^2 for *Au. afarensis* of 2.50 and an EQ^2 of 5.30 for modern humans (de Sousa & Cunha, 2012; Ruff et al., 1997).

Beyond the details added with every new fossil discovery, fossil evidence makes it clear that this increase in hominin brain size did not occur via a continuous, linear trajectory. Just as our thoughts on the course of hominin evolution have changed with the addition of new fossils, so has our understanding of encephalization. The available fossil evidence suggests a period of stasis of hominin evolutionary encephalization between 1.8 million and 600 thousand years before present (Ruff et al., 1997). Additionally, encephalization may have arisen, been accelerated, or inhibited due to the same or differing conditions in various hominin groups. As one example, the modern human and Neanderthal lineages may have achieved high degrees of encephalization by way of differing developmental responses to similar evolutionary pressures (Bruner et al., 2003). As our understanding of the phylogenetic relationships among various fossil taxa improve, the estimated rates and patterns of encephalization for hominin species will require continual revision.

3 | CRANIOFACIAL SKELETAL CORRELATES OF ENCEPHALIZATION

Encephalization is hypothesized to be the primary driver of morphological evolution of the modern human skull, including the suite of traits unique among extant primates of a highly flexed cranial base, domed cranial vault, and retracted facial skeleton (Figure 2). While it is generally acknowledged that increases in relative brain size have played a significant role in the evolutionary development of these cranial traits (e.g., Bastir, Rosas, Stringer, et al., 2010; Bruner, 2007; Bruner, de la Cuétara, Masters, Amano, & Ogihara, 2014; Lieberman, 2011; Lieberman et al., 2004, 2002; McCarthy, 2001; Ross & Henneberg, 1995; Ross, Henneberg, Ravosa, & Richard, 2004; Spoor, 1997), the exact role that encephalization has played in transforming the hominin skull to include these attributes is vigorously debated and studied. Here we discuss three distinct features of skull morphology considered as features that characterize human evolutionary change and summarize the current understanding of the relationship between the evolution of brain size and the emergence of these osseous features.

3.1 | Cranial base flexion

Building upon the work of Virchow (1857) and Ranke (1892) who identified an association between an enlarged human brain and cranial

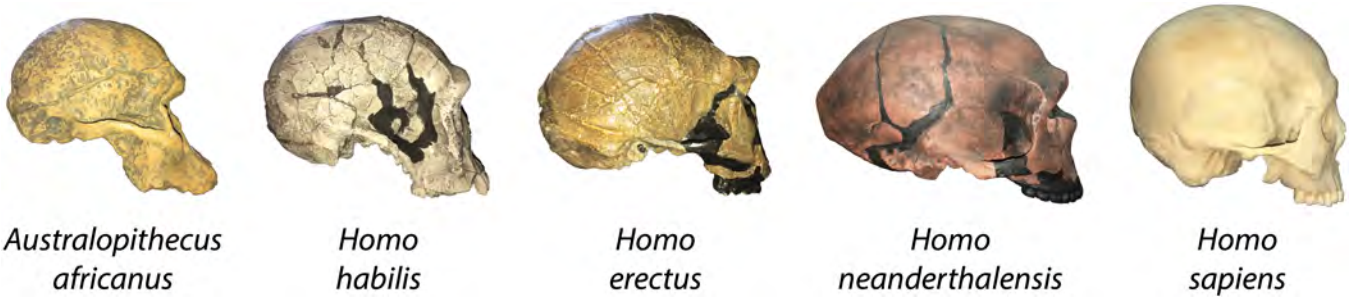

FIGURE 2 Representative hominin fossils showing the progressive intensification of neurocranial globularity, facial retraction, and cranial base flexion with increased encephalization

base morphology, Weidenreich (1941) concluded that the characteristically high degree of flexion in the human cranial base was a direct consequence of a larger brain. Cranial base flexion refers to the degree of angulation along the midline of the cranial base (Figure 3). Biegert (1957, 1963) more formally predicted a correlation between increasing brain size and decreasing cranial base flexion. Though there are other ways to increase skull size, these studies are based on a model of the skull as a closed box with moveable internal parts. An expanding brain can only continue to grow if more room can be made inside that box. One way to increase the size of the box is to increase basicranial flexion. Ross and Ravosa (1993) were the first to refer to this relationship as a "spatial packing" problem and statistically tested Biegert's "spatial packing hypothesis" with a comparative study of nonhuman primate species, finding a significant correlation in haplorrhines between a larger brain (relative to basicranial length) and increased basicranial flexion, but this relationship was not significant among hominoids. A follow up study of modern humans and fossil hominins similarly found a lack of significant correlation between relative brain size and basicranial flexion (Ross & Henneberg, 1995).

While having more highly flexed basicrania than nonhuman primates, fossil hominins seemed to have attained levels of modern human basicranial flexion despite wide variations in relative brain sizes (Bastir & Rosas, 2009; Ross & Henneberg, 1995). Based upon regression analyses of haplorrhines and primates, Ross and Henneberg (1995) found that modern humans actually have cranial bases that are less flexed than expected. Attributing this finding to constraints on the amount of basicranial flexion physiologically possible below 90°, Ross and Henneberg (1995) concluded that some other unknown mechanism for accommodating an enlarged brain must have enabled continued encephalization along the hominin lineage. However, depending on exactly how cranial base flexion is quantified, it is possible that the degree of human basicranial flexion may not be significantly different than expected (Lieberman, Ross, & Ravosa, 2000; McCarthy, 2001; Ross et al., 2004; Spoor, 1997). Estimates of the amount of variation in primate basicranial flexion that can be explained by relative brain size range from 36–58% (Bastir, Rosas, Stringer, et al., 2010; Lieberman, Ross, & Ravosa, 2000; Ross & Ravosa, 1993), leaving room for additional explanatory mechanisms. While it has also been proposed that basicranial flexion is evolutionarily linked with locomotor or postural patterns, this association has repeatedly been refuted in favor of a correlation between basicranial flexion and brain size along the hominin lineage (Biegert, 1963; Lieberman, Ross, & Ravosa, 2000; Ross & Ravosa, 1993; Strait & Ross, 1999; Villamil, 2017).

Lieberman, Hallgrímsson, Liu, Parsons, and Jamniczky (2008) provided an expanded "three-dimensional" (3D) spatial packing hypothesis, adding in considerations of the potential effects of widths in the cranial base, influence of facial length and size on cranial base angle, and both neural and facial constraints on cranial base flexion. Notably, multiple predictions based on this 3D spatial packing hypothesis were experimentally tested utilizing a variety of mouse models, including the *mceph* strain with a mutation that produced a significant increase in brain size. These *mceph* mutants provided a direct, experimental test of how a larger brain might affect cranial bone morphology, and the results confirmed the prediction of a significantly more flexed adult cranial base (Lieberman et al., 2008).

Studies of prenatal and early postnatal human skull growth to resolve the questions regarding the effects of human encephalization on cranial base flexion have produced conflicting results. In contrast to the previously discussed research on adult extant primate, modern human, and fossil hominin specimens showing correlations between increases in brain size and increases in basicranial flexion, data show that the exponential prenatal and early postnatal growth of the brain does not result in a progressive increase in cranial base flexion. The cranial base undergoes temporally dynamic phases of flexion and retroflexion throughout embryonic, fetal, and postnatal development, as it responds to prenatal and postnatal brain and skull growth (Jeffery & Spoor, 2002; Lieberman & McCarthy, 1999; Neubauer et al., 2010; Zollikofer, Bienvenu, & Ponce de León, 2017). Flexion of the cranial base during early human embryonic growth (Diewert, 1983; Sperber, Sperber, & Guttmann, 2010) is followed by cranial base retroflexion during the fetal period, when slow growth of the cranial base relative to rapid brain growth produces significant increases in relative brain size (Jeffery & Spoor, 2002; Lieberman, 2011). This finding is attributed, at least in part, to circumferential growth of the brain enabled by patent cranial vault sutures during fetal development, reducing spatial constraints that might otherwise result in basicranial flexion (Bastir & Rosas, 2009; Jeffery & Spoor, 2002). An alternative hypothesis, that the prenatal retroflexion of the cranial base is related to the development of the upper airway, has found limited support (Jeffery, 2005; Trenouth & Timms, 1999).

The human cranial base does flex rapidly as the brain continues to grow during the first several years of postnatal life. This postnatal flexion is hypothesized to be unique to hominin craniofacial development,

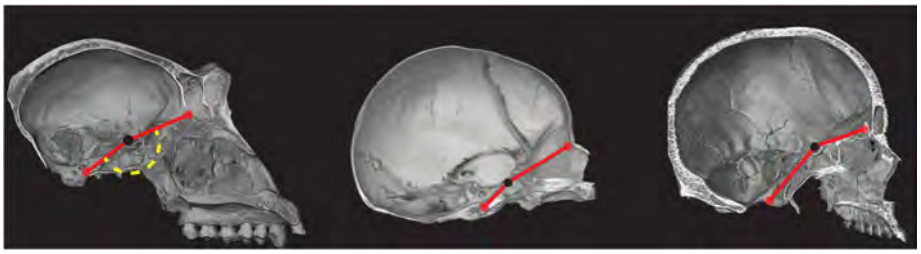

FIGURE 3 Cranial base angle shown on a sagittal section of 3D reconstruction of adult gorilla (left), human neonate (center), and adult human (right). Though diverse measures have been proposed to estimate cranial base angle (solid red line), we show the angle constructed using the landmarks basion, sella, and foramen caecum, with sella as the vertex of the angle (black circle), with the angle measured on the ventral side (dotted yellow line)

as this morphological change is not seen in nonhuman primates (Lieberman & McCarthy, 1999; Neubauer et al., 2010). The transition from prenatal cranial base extension or retroflexion to postnatal flexion may reflect the reducing patency of cranial vault sutures and the sequence of fusion of cranial base synchondroses, the primary sites of anterior–posterior growth (Figure 4). Of the three cranial base synchondroses in humans, the midsphenoidal synchondrosis fuses first during the fetal period (potentially allowing for fetal retroflexion), while the spheno-ethmoidal synchondrosis remains patent for up to 6 years allowing for postnatal flexion (Jeffery & Spoor, 2002; Lieberman & McCarthy, 1999). The spheno-occipital synchondrosis remains patent through adolescence, permitting further cranial base elongation.

The apparent conflicts between the initial tests of the spatial packing hypothesis, correlations between brain size and cranial base flexion, and subsequent studies of prenatal development can be resolved by considering developmental context. Cranial sutures and many synchondroses remain patent during *prenatal* growth when neural tissues are growing exponentially. Importantly, Bastir and Rosas (2009) recognized that much of the original work on the spatial packing hypothesis was premised on the study of *adult* skulls (Biegert, 1963; Ross et al., 2004; Ross & Henneberg, 1995; Ross & Ravosa, 1993). As growth progresses from prenatal to postnatal, the bones that border cranial vault sutures begin to oppose each other, reducing their growth potential, intensifying spatial constraints, and reducing the degree of accommodation possible for the still-developing brain (Bastir & Rosas, 2009; Neubauer et al., 2010; Opperman, 2000; Zollikofer et al., 2017), thereby possibly shifting the burden of accommodation to the cranial base. This realization helps align the previously conflicting studies that considered basicranial flexion by analysis of prenatal versus postnatal specimens but also serves to change the focus from postnatal morphology to how prenatal growth might influence cranial base flexion.

3.2 | Cranial vault globularization

Remarkable accommodation and conformity of the outer surface of the brain and the endocranial surface of the neurocranium is evident across living and extinct vertebrates and throughout development of extant vertebrate species (Richtsmeier & Flaherty, 2013). Evidence for this tight correspondence is also seen in diseases of the craniofacial complex (Richtsmeier et al., 2006). Experimentally, Moss and Young recognized from comparisons of hydrocephalic and microcephalic rats that an increase in the volume of intracranial contents resulted in a more domed or globular cranial vault (Moss & Young, 1960). Cranial vault morphology is likely to result from multiple inputs, including a relatively larger brain, smaller cranial base, and smaller face (Lieberman et al., 2002; Zollikofer et al., 2017). Early work on head form patterns by Enlow found associations between more rounded or spherical braincases and highly flexed cranial bases (Enlow & Hans, 1996; Enlow & McNamara, 1973). The mechanistic basis for variation in cranial vault globularity remains to be fully addressed; however, recent work has suggested that cranial globularity may have played an important role in the variation of Neandertal and other fossil hominin cranial forms (Bastir, 2018; Bastir et al., 2010).

In modern humans, the cranial vault has already taken on its species-specific globular shape by birth. The continuing expansion of the parietal region and cerebellar fossa relative to other portions of the skull contribute to the early postnatal "globularization phase" (Neubauer et al., 2010; Zollikofer et al., 2017). While a globularization phase has been proposed to be unique to humans (Gunz et al., 2012; Gunz, Neubauer, Maureille, & Hublin, 2010; Neubauer et al., 2010), recent ontogenetic and morphological analyses of nonhuman primates have shown that a pattern of endocranial development that increases the roundness of the cranial vault may actually be a shared ancestral feature among great apes that has been retained in humans, gorillas, and orangutans but lost during *Pan* evolution (Zollikofer et al., 2017). Though compared to chimpanzees humans have a smaller brain at birth relative to adult brain size (DeSilva & Lesnik, 2006), during the perinatal phase humans already have a flexed cranial base and globular cranial vault, while chimpanzees have an extended cranial base and elongated cranial vault (Neubauer et al., 2010).

The globularization of the human skull during perinatal development results from changes in the shape of the cranial vault bones and underlying brain (Bruner, 2004; Bruner et al., 2003; Hofer, 1969; Lieberman et al., 2002; Neubauer et al., 2010; Weidenreich, 1941). During the perinatal phase (birth to 1 year), the parietal lobes of the brain expand relative to the occipital and temporal regions, resulting in further bossing of the parietal bones and an increasingly globular neurocranial appearance (Neubauer, Gunz, & Hublin, 2009). An age-graded ontogenetic comparison of human and chimpanzee endocasts found that at all postnatal developmental stages, human endocasts were characterized as being more globular in shape relative to chimpanzee endocasts, and this difference was presumed to result from species-specific differences in early brain development when neural

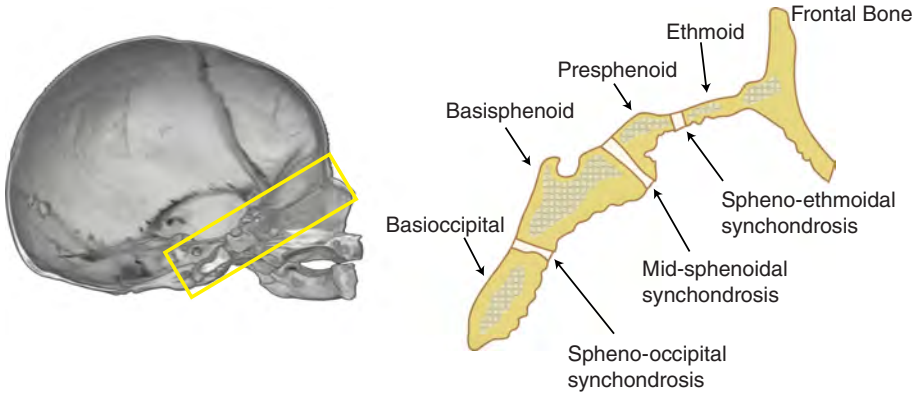

FIGURE 4 3D reconstruction of computed tomography images of a human neonate (left) showing positioning of cranial base synchondroses (yellow box). Illustration of a sagittal section (right) of the human cranial base showing individual bones and synchondroses

growth rates are high and cranial ossification is incomplete (Neubauer et al., 2010).

Similar distinctions have been found between modern humans and fossil hominins. Despite similar brain sizes, Neanderthals and modern humans differ in neurocranial globularity (Gunz et al., 2010; Gunz et al., 2012). In archaic and Neanderthal specimens, an enlarging brain is characterized by a reduction in the occipital lobes, enhancement of vertical development, and a shortening of the parietal chord (Bruner et al., 2003). Neanderthals also have significantly smaller cerebellar regions than modern humans (Kochiyama et al., 2018). In contrast, endocasts of anatomically modern humans exhibit parietal lobe development characterized by a lengthening of the parietal chord and orthogonal growth of the midsagittal profile, which ultimately produces a more globular shape (Bruner, 2004, 2008). Recent analyses have additionally demonstrated that modern human brains have significantly larger parietal regions compared to Neanderthals (Kochiyama et al., 2018). While having similar absolute brain sizes at birth, perinatal Neanderthal specimens are distinct from modern humans at birth due to a more elongated cranial vault with flatter parietal and occipital bones (Gunz et al., 2012). The additional globularization phase occurring after birth that occurs in modern humans further contributes to the pronounced differences in skull morphology between adult Neanderthals and modern humans, potentially driven by species differences in brain growth rates and timing (Gunz et al., 2010, Gunz et al., 2012).

Another potential explanation for the globular shape of the human cranial vault has been proposed as part of a "wiring" hypothesis, wherein the shape of the human brain is attributed to the need to reduce the wiring length (distance between axon and neuron to form functional circuits), both within the telencephalon and between the cerebrum and diencephalon (e.g., Bruner, Martin-Loeches, & Colom, 2010; Chklovskii & Stevens, 2000; Hofer, 1969; Lieberman, Ross, & Ravosa, 2000; Mitchison, 1991; Ross & Henneberg, 1995; Sporns, Chialvo, Kaiser, & Hilgetag, 2004; Van Essen, 1997). This idea can be traced to Santiago Ramón y Cajal and is not specific to the explanation of human brains, as it has been applied across species (Rivera-Alba et al., 2011; Stevens, 2012). Some scholars have hypothesized that a more spherical cerebrum would optimize neural connectivity of axons and dendrites within the evolutionarily expanded hominin neocortex (Bruner, 2004; Lieberman, Ross, & Ravosa, 2000; Ross & Henneberg, 1995). The location of the cerebellum and brain stem would anatomically prevent expansion of the neocortex in a posterior or inferior direction, making anterior expansion the path of the least resistance. To produce a more balanced spherical shape alongside the anterior neocortical expansion, the brain necessarily develops a "kink", or ventral brain flexion (Lieberman, Ross, & Ravosa, 2000). While neocortical anterior expansion could occur without such brain flexion or other accommodations, the result would be an unbalanced, anteroposteriorly longer head (Jerison, 1982). Though detailed maps of brain circuitry are now available for adults of many species, how the mechanisms that underlie wiring that occurs early in brain development contribute to the production of overall brain shape variation is not known.

3.3 | Facial skeleton orientation and projection

One of the primary differences between archaic hominins and anatomically modern humans relates to the retraction of the facial skeleton (Lieberman et al., 2002). However, questions remain regarding whether retraction of the modern human facial skeleton is a consequence of (a) encephalization, (b) modifications to the cranial base, or (c) an independent trend that occurred simultaneously with human encephalization and cranial base modifications (Bastir, 2008). Due to its anatomical location as an architectural interface between the developing brain and face, the cranial base is often cited as playing a critical role in the evolution of human facial morphology, including reduced facial projection and prognathism (e.g., Bastir, 2008; Bastir & Rosas, 2016; Enlow, 1990; Lieberman, Pearson, & Mowbray, 2000).

One model that combines the influence of encephalization and cranial base morphology on facial architecture is the "facial block rotation model." This model links relative increases in brain size along the human evolutionary trajectory with a concurrent reduction in mid-facial projection and maxillary prognathism (Bastir & Rosas, 2016; Lieberman, 2011; Lieberman et al., 2002; Lieberman, Ross, & Ravosa, 2000; McCarthy & Lieberman, 2001). Essentially, a highly flexed cranial base is hypothesized to cause a rotation such that the face becomes tucked underneath the anterior cranial base, reducing facial

projection. While studies of both 2D and 3D morphology provide support for this hypothesis (McCarthy & Lieberman, 2001; Neaux et al., 2013), at least one recent analysis suggests that it is the overall *orientation* of the cranial base, rather than midsagittal flexion, that influences facial orientation (Bastir & Rosas, 2016). The relationship between cranial base flexion and facial block rotation appears to be unique to humans. A study of extant great apes confirmed the positive correlation between increased cranial base flexion and downward rotation of the facial block in modern humans, a weaker positive relationship in *Pan*, and no significant relationship in *Gorilla*, resulting in the characteristic orthognathic face of modern humans (Neaux et al., 2013). Of note, each of these studies attempting to link either brain size or cranial base flexion with facial orientation and projection examines a correlation between these morphologies, rather than providing a mechanistic explanation.

Additionally, the relationship between midline and lateral cranial base elements has been hypothesized to play a role in facial retraction. Bastir and Rosas (2016) found that covariation between both midline and lateral cranial base features and alveolar prognathism and facial proportions may represent a shared primitive relationship within the hominin skull. While Lieberman (1998) proposed that a midline shortening of the sphenoid contributed to modern human facial retraction, other evidence challenges this view with findings that the modern human midline sphenoid is actually longer compared to Neanderthals and mid-Pleistocene hominins (Bastir & Rosas, 2016; Spoor, O'Higgins, Dean, & Lieberman 1999). Instead of relative length, the positioning of the sphenoidal body relative to the wings appears to be a significant contributor to the degree of facial projection (Bastir & Rosas, 2016).

Importantly, multiple studies agree that distinguishing features of the human facial skeleton are established early in ontogeny, most likely during prenatal growth. Morphological and ontogenetic studies have found that features characteristic of Neanderthals and absent in modern humans, including midfacial projection and prognathism, likely are a result of differential rates of prenatal growth or changes in early postnatal osteogenic growth fields of the various cranial components (Gunz et al., 2012, 2010; Maureille & Bar, 1999; Ponce de León & Zollikofer, 2001; Ponce de León & Zollikofer, 2006; Zollikofer & Ponce de León, 2010). Studies comparing humans and nonhuman primates have similarly established that distinct facial morphologies and trajectories, including midfacial prognathism, are already in place at birth (Mitteroecker, Gunz, Bernhard, Schaefer, & Bookstein, 2004; Zumpano & Richtsmeier, 2003). Taken together, these studies support not only the uniqueness of the human face, but also the importance of early developmental processes and prenatal growth in establishing the morphology and developmental trajectories of these distinctly human features.

If encephalization impacts skull morphology, ultimately leading to the evolution of a domed cranial vault, flexed cranial base, and retracted facial skeleton, then it is critical that we understand the early development of both the brain and skull. While there is significant growth during postnatal life, the tissues that form both of these organs differentiate in close proximity responding to some of the same gene networks and continuing to interact throughout their development. Next, we summarize the early developmental dynamics of the brain and skull to highlight specific aspects of their integration and to emphasize the significance of prenatal growth in the production of human skull morphology.

4 | EARLY DEVELOPMENT OF THE BRAIN AND SKULL

Most of the studies summarized above represent analyses of formed or forming skull bones and their hypothesized interaction with the brain. The brain originates early in development from differentiated ectoderm that forms a hollow tube and acquires an exceedingly complex shape over embryonic time. Individual cartilaginous and osseous elements of the skull form on the expanding neural surface from neural crest- and mesoderm-derived mesenchyme that eventually unite to form a skull that supports and protects the brain, other cranial soft tissues, and functioning spaces. As the development of each of these tissues is incredibly complicated, we focus on those aspects of these early growth processes that are critical to the formulation of logical hypotheses about the developmental interaction of brain and skull that leads to phenotypic variation and potentially to evolutionary change.

4.1 | Prenatal development of the brain

In humans, brain growth and development begin early during gestation and continues after birth. Peak brain growth velocity is achieved just prior to birth (Halley, 2017), with human neonatal brain weights averaging approximately 360–380 g (Dekaban & Sadowsky, 1978; DeSilva & Lesnik, 2008; Ho, Roessmann, Hause, & Monroe, 1981). Brain growth continues postnatally, but follows a decelerating decay curve (Halley, 2017; Halley & Deacon, 2017). Maximum brain weight and high rates of synapse formation, myelination, and dendritic development are reached during postnatal life, while gradual declines in weight begin around age 45–50 (de Graaf-Peters & Hadders-Algra, 2006; Dekaban & Sadowsky, 1978). Despite intrauterine growth accounting for only 25–30% of adult brain weight (DeSilva & Lesnik, 2006), the prenatal development of the brain is the predominant time for the differentiation of neural tissue and neurogenesis, particularly within the cerebral cortex.

The brain develops from the neural plate, a thickened portion of ectoderm located on the dorsal surface of the embryo, the rostral end of which is most apparent. Neurulation begins when the neural plate folds longitudinally to form a midline groove along its rostro-caudal axis (Figure 5a). The neural tube takes shape as the neural folds, ridges that form on either side of the neural plate, rise up, fold inward, and begin to fuse at the center, forming a tubular structure (Stiles & Jernigan, 2010). As the neural tube elongates with growth of the embryo, the tube expands radially due to rapid cell division (see below) and flexes ventrally, with regions growing at differing rates to create three obvious bulges at the rostral end. These are the primary vesicles: the prosencephalon (future forebrain), mesencephalon (future midbrain), and rhombencephalon (future hindbrain) (Figure 5b). As radial growth continues, specific areas of the primary vesicles differentiate to take on regional identities with specific functions. Interestingly, these

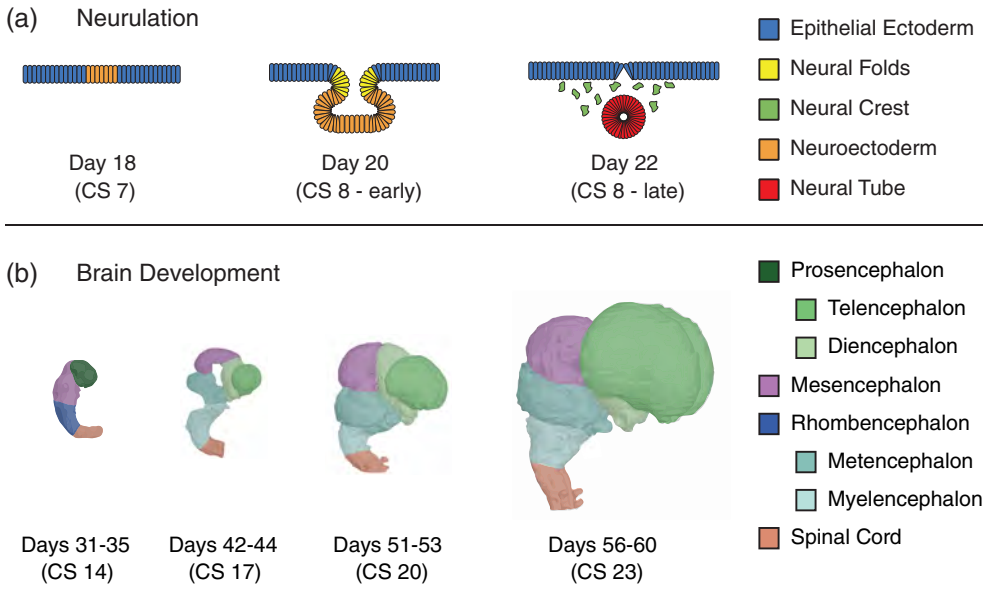

FIGURE 5 Brain development. (a) Early development of neural tube from neuroectoderm (adapted from Richtsmeier & Flaherty, 2013). (b) Morphogenesis of brain from neural tube and formation of major brain regions (adapted from Shiraishi et al., 2015). CS = Carnegie stage

regions are defined before the first axons appear, suggesting that the regions and the distinct combination of transcription factors and adhesion molecules that they express contribute to guiding axon connectivity and establishing brain wiring (Chédotal & Richards, 2010).

The alar plate of the prosencephalon expands to form the telencephalon that will form the cerebral hemispheres, while the basal plate becomes the diencephalon. The diencephalon, mesencephalon, and rhombencephalon contribute to the brain stem that continues to flex at the mesencephalon. The rostral portion of the rhombencephalon differentiates into the pons and cerebellum, while the caudal portion forms the medulla oblongata. By 50 days of gestation (roughly 7 weeks), the rudimentary architecture of the human brain is established (Richtsmeier & Flaherty, 2013; Stiles & Jernigan, 2010) (Figure 5b).

Once fusion of the neural tube is complete and elongation and radial expansion of the tube is underway, neuroepithelial cells line the interior of the neural tube, with the hollow portion eventually contributing to the ventricular system of the brain (Götz & Huttner, 2005; Stiles & Jernigan, 2010). As neurogenesis begins, the neuroepithelium gives rise to radial glial cells and is responsible for the initiation of a specific radial migration of neurons that results in the formation of a multilayered cortex (Götz & Huttner, 2005; Noctor, Martínez-Cerdeño, Ivic, & Kriegstein, 2004; Stiles & Jernigan, 2010). Signaling factors on the surface of the radial glia cells guide the migration of neurons produced in the ventricular zone radially toward the outer surface of the neural tube in complex waves of unique sets of neurons that result in cortical layers organized in an "inside-out" fashion (Götz & Huttner, 2005; Kwan, Sestan, & Anton, 2012; Noctor et al., 2004; Stiles & Jernigan, 2010).

Prior to neurogenesis, the majority of the ventricular zone radial glial cells undergo symmetrical divisions, producing two intermediate progenitor cells, thus exponentially increasing the progenitor cell pool and the potential number of neurons (Kwan et al., 2012; Noctor et al., 2004; Pinto & Gotz, 2007). Once neurogenesis begins, differing cells undergo several types of divisions: symmetrical divisions producing two intermediate progenitor cells, asymmetrical divisions producing one intermediate progenitor cell and one neuron, and ultimately terminal symmetrical divisions that produce two neurons (Götz & Huttner, 2005; Kwan et al., 2012; Noctor et al., 2004; Pinto & Gotz, 2007). Although the development, differentiation, and refinement of the brain proceeds along a gradual and continuous pathway throughout the first two decades of postnatal life (Stiles & Jernigan, 2010), the details of prenatal development of the brain provide the map for all future development.

Embryonic development of the brain is characterized by dynamic changes in external appearance (increase in size; flexion/extension and change in shape of various regions) that corresponds with internal organogenesis (Huang et al., 2009; Nolte, 2009; Shiraishi et al., 2015). Magnetic resonance microscopy of 3D dynamics and morphology of the human embryonic brain have revealed eccentric (without thickening of brain tissue) and concentric (resulting in brain tissue thickening) growth dynamics (Shiraishi et al., 2015). Each part of the brain grows at different rates during the embryonic and fetal periods (Nolte, 2009). The arrangement of these regions and their disproportionate growth result in the brain taking on an increasingly flexed morphology by week 8 (Carnegie stage 23) (Nolte, 2009; Shiraishi et al., 2015). Surface mapping by tissue thickness enabled simultaneous visualization of surface morphology and internal thickness and demonstrated a correlation between the flexion and extension of the forming brain and tissue thickness (Shiraishi et al., 2015). Tissue became thicker in the regions of brain flexion, while it remained thin in the regions of extension, suggesting that intrinsic growth dynamics contribute to the formation of various brain flexures (Shiraishi et al., 2015).

While the brain continues to grow postnatally, the degree of brain organization and size achieved prenatally is specific to humans and is

critical to human evolution and encephalization. A newborn chimpanzee brain weighs only 150 g, but this already constitutes nearly 40% of adult chimpanzee brain mass (DeSilva & Lesnik, 2006, 2008). In comparison, a modern human neonate brain weighs approximately 380 g, more than twice that of a chimpanzee but represents only 28.6% of the average adult human brain mass (Dekaban & Sadowsky, 1978; DeSilva & Lesnik, 2008). Due to a slightly longer gestational period in humans relative to chimpanzees, at least part of the difference in absolute neonatal brain size can be attributed to the *longer duration* of prenatal brain growth, although the main contributor to the larger human neonatal brain is a faster prenatal *rate of growth* (Neubauer, 2015). Postnatal growth also contributes to the unique degree of human encephalization, whether through species-specific differences in postnatal growth grates or an extended duration of human postnatal brain growth (Halley, 2017; Halley & Deacon, 2017; Leigh, 2004; Passingham, 1985). However, it is the prenatal growth of the human brain that provides the foundation for initial skull formation and growth.

4.2 | Prenatal development of the skull

Evolutionarily and developmentally, there are two skulls; one derived from the endoskeleton that forms initially, and the other from the exoskeleton that forms relatively later during embryogenesis. The cranial endoskeleton is initially formed in cartilage and, when ossified, is composed primarily of cartilage bone that mineralizes by endochondral ossification (Kawasaki & Richtsmeier, 2017). The cranial exoskeleton, also called the dermatocranium, is composed of dentin, enamel, and intramembranously forming dermal bone that eventually encases the cranial endoskeleton in adults (Kawasaki & Richtsmeier, 2017) (Figure 6).

Mesenchymal cells from two sources—neural crest and mesoderm—serve as osteochondro progenitor cells capable of differentiating into chondroblasts to form cartilage and/or osteoblasts to form bone, depending upon the signals they receive and to which they can respond (Long, 2012). The earliest signs of skull formation occur with the condensations of chondroblasts that secrete matrix ventral to the base of the brain to form elements of the two major components of the cranial endoskeleton: the chondrocranium (Kawasaki & Richtsmeier, 2017) and the pharyngeal skeleton (Frisdal & Trainor, 2014). The chondrocranium is that part of the endoskeleton that protects the brain and three principal sense organs (Kawasaki & Richtsmeier, 2017), while the pharyngeal skeleton is that part of the endoskeleton that protects the lower aspect of the oral cavity and neck region, providing support for the organs within. A multitude of cartilages rapidly form from condensations of chondroblasts until a relatively solid series of cartilages make up the chondrocranium. In humans, cartilage formation of the spheno-occipital area of the brain case floor begins in the 7^{th}–8^{th} gestational week, and most of the chondrocranial cartilages are established by 9 weeks (Tubbs, Bosmia, & Cohen-Gadol, 2012). Elements of the chondrocranium include the brain case floor, lateral wall and roof of the occipital region, lateral wall and roof of the pre-occipital region, olfactory region, and otic region.

Importantly, cartilage can grow by accretion and interstitially, allowing it to expand in size and rapidly change in shape to accommodate growing cranial soft tissues and functional spaces. The chondrocranium ossifies primarily by endochondral ossification, though membrane bone may have replaced some cartilage bone in certain lineages having secondarily lost their original cartilaginous stage (Bellairs & Gans, 1983; Kawasaki & Richtsmeier, 2017). The formation of a cranial skeleton that responds to continuously changing shapes of the adjacent embryonic tissues and spaces seems implausible without an initial cartilaginous framework that is capable of interstitial growth, but that framework is rapidly replaced by bone as the organism matures. As portions of the chondrocranium ossify endochondrally, key areas capable of accelerated growth remain unmineralized, including several synchondroses, where growth extends from a central zone of growing cartilage bordered by endochondral osteogenic fronts (Flaherty, Singh, & Richtsmeier, 2016; Lieberman, 2011). These include the spheno-ethmoidal, mid-sphenoidal, and spheno-occipital synchondroses (Figure 4).

Dermal bone of the dermatocranium is not preformed in cartilage but forms directly through intramembranous ossification involving the differentiation of osteoblasts and direct secretion and subsequent mineralization of bone matrix (Kawasaki & Richtsmeier, 2017). Areas of initial ossification are the result of osteoprogenitor cells migrating to form condensations in which they proliferate, differentiate into osteoblasts that secrete osteoid, and subsequently mineralize the matrix to form an "ossification center." As bone continues to mineralize at the center, zones of active osteoblast differentiation known as "osteogenic fronts" define the periphery of developing cranial dermal bones (Opperman, 2000; Tubbs et al., 2012). Bones of the dermatocranium form in specific locations such that postnatally, skull bones protect specific areas of brain surface anatomy representing functional primary areas of the cortex: the motor area (part of the frontal cortex) is covered by the frontal bone; the somatosensory area (part of the parietal cortex) is covered by the parietal bone; and the primary visual area (visual cortex) is covered by the occipital bone (O'Leary et al., 2007). Whether this arrangement, which is largely conserved across mammals, is simply anatomical or is of developmental or functional significance is not known. In humans, the initial ossification centers for the cranial vault bones begin to appear during the 8^{th}–9^{th} gestational week on the outer surfaces of edges of some of the chondrocranial cartilages (Kawasaki & Richtsmeier, 2017; Sperber et al., 2010).

As cranial vault bones expand, osteogenic fronts that border areas of mesenchyme that spatially separate the bones approach one another and eventually form sutures. Cranial sutures are fibrous joints that consist of two osteogenic bone fronts and an intervening cellular mass of undifferentiated mitotic mesenchymal cells, all of which are bounded by the surface of the osteogenic layer (superficial) and the external surface of the dura mater (deep), and function as bone growth sites (Flaherty et al., 2016; Opperman, 2000). As the brain grows, cranial bones are pushed away radially while adding bone by the differentiation of osteoblasts along the length of the bone front (Opperman, 2000; Tubbs et al., 2012). Signaling networks discourage mesenchymal cells in the suture from differentiating into osteoblasts and maintain suture patency, enabling further growth of individual bones and of the cranial vault as a whole (Flaherty et al., 2016; Opperman, 2000; Tubbs et al., 2012). The presence, specific location, and patency of cranial sutures is thought to be influenced by the early growth and development of the brain, including signals emanating from (or mediated through) the dura mater (Opperman,

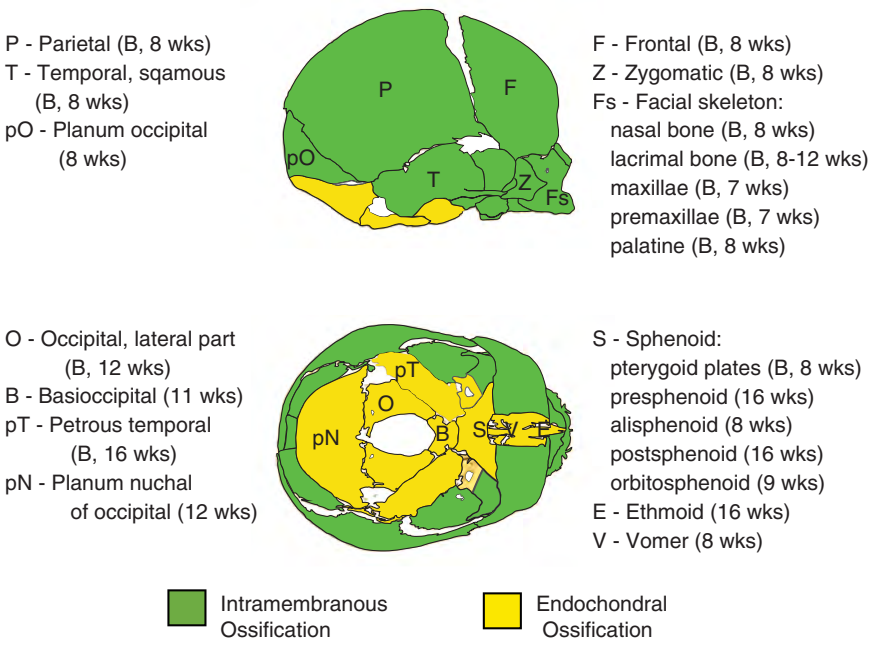

FIGURE 6 3D reconstruction of computed tomography images of a newborn modern human skull indicating mode of ossification (adapted from Flaherty et al. 2016) and showing timing of mineralization of individual skull elements (see Sperber et al., 2010). B = bilateral

2000; Opperman, Passarelli, Morgan, Reintjes, & Ogle, 1995; Opperman, Sweeney, Redmon, Persing, & Ogle, 1993; Tubbs et al., 2012).

4.3 | Integration of the brain and skull

Evidence exists, both theoretical and experimental, to support the tightly integrated relationship between the brain and skull throughout ontogeny (Enlow, 1990; Moss & Young, 1960; Richtsmeier et al., 2006). The interaction of brain and skull development is facilitated by biophysical forces and molecular signaling, especially during prenatal and early postnatal ontogeny, when cranial bones are dynamically forming, and sutures and synchondroses are still patent and sufficiently flexible to adapt quickly to the exponential growth of neural tissues. Biophysical forces play a significant role in the early development of the brain and skull. Moss and Young (1960) formulated the "functional matrix hypothesis (FMH)" that proposed a biomechanical relationship between the meninges, brain, and skull. They observed that the dura mater is attached to the endocranial surface of the skull at several points and hypothesized that the growing brain places a mechanical strain on the dura mater that is transmitted to osteogenic cells on the endocranial surface, thus influencing skull shape (Moss & Young, 1960). The FMH remains an important step in the consideration of how strain produced by the growing brain might affect the developing cranial bones, but these ideas have yet to be tested using modern technologies capable of more direct measurement of material properties and mechanical forces of embryonic cells and tissues.

While the FMH produced important insight on the potential effects of physical interactions of the brain, meninges, and skull, the mechanism proposed was purely biomechanical as the interplay between biophysical forces, molecular signaling, and developmental genetic pathways were not yet realized. Modern experimental evidence shows that biophysical forces, including those generated by growing soft tissues, can impact the behavior of molecules and cells (Chan, Eoh, & Gerecht, 2018; Clause, Liu, & Tobita, 2010; Ikegame et al., 2001; Maul, Chew, Nieponice, & Vorp, 2011; Palomares et al., 2009). The brain also acts as an architectural support for components of the developing face, with the early embryonic positioning of the facial prominences determined by the position and rate of growth of the developing neural tube (Marcucio, Hallgrimsson, & Young, 2015; Marcucio, Young, Hu, & Hallgrimsson, 2011). Moreover, molecular signaling between the brain and facial compartments indicate that the forebrain may direct species-specific facial ontogenetic trajectories, potentially through Sonic hedgehog (Shh) signaling between the brain and ectoderm (Adameyko & Fried, 2016; Marcucio et al., 2015, 2011).

While the number of experiments one can conduct with animal models is limited, computational modeling provides infinite ways to explore the role of biomechanics of brain growth in the differentiation of cells destined to form cranial vault bones and the sutures that form between them. Lee and coworkers proposed a mechanobiological model for the formation of cranial vault bones and sutures, coupling structural mechanics of changing embryonic brain morphology with reaction–diffusion equations (Turing, 1952) that describe the interaction of two molecules (an activator and an inhibitor) supervising the differentiation of osteoblasts (Lee, 2018; Lee, Richtsmeier, & Kraft, 2017). The mechanobiological model predicts some key features of cranial vault bone formation, including the relative location of ossification centers of the individual vault bones, the pattern of cranial vault bone growth over time, and the location of cranial vault sutures (Lee, 2018). Other computational approaches, including anatomical network model analyses, suggest that brain growth contributes more to morphological changes in the cranial base and vault, while unconstrained bone growth and the bony network architecture of the

human skull alone may be sufficient to explain the formation of sutures and boundaries between bone in these cranial modules (Esteve-Altava & Rasskin-Gutman, 2014; Esteve-Altava, Vallès-Català, Guimerà, Sales-Pardo, & Rasskin-Gutman, 2017). Though much work remains, the results of these studies suggest that mechanical strain from the growing brain contributes information to specific aspects of cranial vault formation and that morphology, specifically change in morphology due to growth, is a fundamental mechanism of craniofacial development. Future efforts in computational modeling can help identify and test additional mechanisms underlying shape change of the skull during development and evolution.

All tissues have distinct intrinsic physical properties that are important in their structure, function, and growth. The mechanical properties of cartilage and bone on the one hand, and neural tissue on the other hand, exist at two extreme ends of any measure of stiffness. However, there are several issues to consider when contemplating the influence of brain growth on the developing skull or whether the characteristics of skull morphology and growth impact brain shape. First, most measures of biological tissues are conducted on adult specimens, and it is well known that material properties of embryonic or immature tissues are unlike the properties of adult tissues (e.g., Gefen, Gefen, Zhu, Raghupathi, & Margulies, 2003; Mikic, Isenstein, & Chhabra, 2004; Tanck et al., 2004), and we are only beginning to develop the technology to measure these aspects of embryonic tissues precisely (e.g., Chan et al., 2018; Pillarisetti et al., 2011). Second, although the brain is clearly less stiff to the touch relative to cartilage or bone, experiments have demonstrated that brain tissue is incompressible due to its hydrated nature (Libertiaux, Pascon, & Cescotto, 2011). For example, the majority of experimental evidence does not support the idea that folding of the cerebral cortex is a response to mechanical constraints imposed by the surrounding meninges and skull (Welker, 1990), but instead lie in mechanical forces that arise during brain development and originate at the cellular level (Kroenke & Bayly, 2018). Finally, we stress that the important interactions that might influence the changing shape of the growing brain or guide the skull to adapt to the brain's changing shape occur at the level of the cell. Though beyond the scope of what can be presented here, physical forces, extracellular matrix properties, and cell-to-cell contact contribute significantly to cell fate decisions and cellular responses (Clause et al., 2010), though the mechanisms by which mechanical signals are transduced are not well known. The influence of physical and soluble factors do not operate in isolation but are influenced by aspects of systems biology including tissue-specific patterns of ligand and receptor expression (Discher, Mooney, & Zandstra, 2009).

Morphological integration (Olson & Miller, 1958), assessed by statistical analysis of covariance patterns between phenotypic traits, is a quantitative approach to understanding the production of morphological variation through the study of the modular nature of phenotypes. This approach has been used to understand how various skull modules (e.g., cranial vault, base, and facial skeleton of skull; anterior alveolar and posterior articulating parts of mandible) interact during development and evolution (e.g., Cheverud, 1982, 1995; Hallgrímsson, Willmore, Dorval, & Cooper, 2004; Klingenberg, 2010; Klingenberg, Mebus, & Auffray, 2003; Martínez-Abadías et al., 2011). These studies focus on the skull in isolation from the brain and other soft tissues, in part because most museum samples consist largely of skeletal (sometimes fossilized) remains, but also because our concepts of modules are based primarily on adult skulls and on anatomical categories that conceptualize hard and soft tissues as separate systems. To date, few studies have combined differing tissues in the study of the covariation structure of phenotypes (see below), though some have considered the integration of modules of the cranial and postcranial skeletons (Villamil, 2018).

Modern approaches to the study of development recognize that intersecting hierarchies of genetic regulatory networks and developmental processes serve as organizing mechanisms, but only a few have investigated the effect of genetic variants on the covariation structure of multiple tissues using controlled experimental data (Martínez-Abadías et al., 2013; Motch Perrine et al., 2017). As several signaling pathways contribute to the development of both neural and skeletal tissues (e.g., fibroblast growth factors [FGF], transforming growth factor [TGFβ], wingless-related integration site [Wnt] [Richtsmeier & Flaherty, 2013]), we know that cells destined to become brain and skull respond to many of the same genetic inputs. Interactions of these signaling systems and the tissues that they pattern are fundamental to the consistent but labile functional and structural association of brain and skull conserved over evolutionary time. However, as cells become further differentiated, eventually contributing to either skull or brain, the properties of the cells change, as does their ability to respond to a detected signal (e.g., by changing size or shape, further differentiation, death, or division). As a cell's ability to detect or respond to particular genetic signals changes with differentiation, the potential integrating properties of these signaling pathways across tissues may be stronger earlier in development.

Consideration of regulatory processes as the basis for module organization does not negate the importance of previous studies focused on covariances among skeletal modules, but adds to the explanation of how and why the covariances (correlations) occur and why they change during ontogeny. If morphological integration theory is correct and modules pattern head formation, then it is likely that the fields specified by module organizers change over developmental time depending upon a shifting hierarchy of the influence of genetic, anatomic, physiological, and biophysical relationships. Additionally, fields specified by regulatory processes are more likely to cross tissue boundaries earlier in development. As cells differentiate and their functions become more specific to the organ they occupy, their ability to respond to signals changes. Consequently, it is likely that brain-skull integration may be the strongest very early in development, a time that has been understudied by anthropologists and that is rarely available for study from fossils. Delineation and confirmation of hybrid-tissue modules that either function together or respond in tandem to network-based regulatory processes (developmental modules) can only be verified by experimental work.

5 | BEYOND THE FOSSIL RECORD: ANIMAL MODELS

While the hominin fossil record and comparative primate data have been used for decades to establish correlations between relative brain size and cranial morphology, true cause-and-effect linkages can only be established through experimental evidence. Determination of cause and effect of these associations requires experimental alteration

TABLE 1 Selected examples of mouse models with target genes associated with changes in brain size and development

Model name/experimental manipulation	Brain characteristics	Citation
nestin^{rtTA}/tetbi^{4D}	Increased surface area of the cerebral cortex	(Nonaka-Kinoshita et al., 2013)
In utero electroporation of Trnp1	Expansion of neocortex	(Stahl et al., 2013)
In utero electroporation of ARHGAP11B	Expansion of neocortex through increased basal progenitors	(Florio et al., 2015)
SmoM2 causing constitutive activation of Shh	Increased neocortical growth	(Wang, Hou, & Han, 2016)
FGF2 microinjection to cerebral ventricles	Increased cortical volume and number of neurons	(Vaccarino et al., 1999)
In utero electroporation of TBC1D3	Increase in outer radial glial cells and produces a folded cortex	(Ju et al., 2016)
Ella;Fgfr3$^{+/K644E}$	Increase in cortical thickness	(Inglis-Broadgate et al., 2005)
In utero electroporation of human FoxP2	Increased number of neurogenic intermediate progenitors	(Tsui, Vessey, Tomita, Kaplan, & Miller, 2013)
BAF170 conditional knock-out	Increased volume and surface area of neocortex	(Tuoc, Narayanan, & Stoykova, 2013)
Mceph/mceph	Postnatal brain enlargement	(Diez et al., 2003)
Casp-3$^{-/-}$ *and casp-9*$^{-/-}$	Increased forebrain progenitor population	(Haydar, Kuan, Flavell, & Rakic, 1999)
Stablizined β-catenin	Increased neuronal production and enlarged forebrains	(Chenn & Walsh, 2003)
Hs-HARE5::Fzd8	Increased brain size	(Boyd et al., 2015)

of a few key, controlled variables—approaches that are neither ethically nor experimentally possible in humans or primates.

A number of experimental model organisms have been used to understand both brain and skull development. Among mammalian models, the mouse is a common choice given a relatively short generation time and low maintenance requirements (Doyle, McGarry, Lee, & Lee, 2012; Perlman, 2016). Despite the evolutionary and genetic distance between mice and *Homo sapiens*, studies have repeatedly confirmed the utility of mouse models in addressing evolutionary and anthropological questions, including tests of hypotheses regarding hominin encephalization (Boughner et al., 2008; Hallgrímsson & Lieberman, 2008; Lieberman et al., 2008; López, Stock, Taketo, Chenn, & Ravosa, 2008). Based on knowledge of the differences in ways genes drive or associate with disease processes in the two species (Perlman, 2016; Seok et al., 2013), questions have arisen about whether a specific genetic mutation in a mouse model could accurately represent potential genetic variants that occurred during human evolution. Though many questions remain, there is a growing body of evidence that suggests that the effects of certain genetic variants operate through developmental pathways that are common across mammals (Hallgrímsson & Lieberman, 2008; Perlman, 2016), and questions of specific function can always be studied for any genetic variant. However, when studying the interactions between brain and skull, we are not interested in the *specific* function of a gene or consequence of a mutation of that gene. Rather, experimental approaches to the question of encephalization and the coupled changes in skull morphology are focused largely on the *relational* principles of organismal design (Weiss, 2005; Weiss & Buchanan, 2004); generalizations that go beyond enumerating specific cases and focus instead on higher order "emergent" results of structure and interaction.

Given the evolutionary importance of encephalization across vertebrates, it is likely that the developmental pathways that structure the interaction between the developing brain and skull are similar across mammals (Hallgrímsson et al., 2004; Hallgrímsson & Lieberman, 2008; Hallgrímsson, Lieberman, Liu, Ford-Hutchinson, & Jirik, 2007; Martínez-Abadías, Mitteroecker, et al., 2012). The specific genetic variants that initiated phenotypic change during human evolution may differ from a mutation present in a mouse model, but their participation in conserved developmental pathways ultimately will produce similar phenotypic outcomes valuable for our understanding of evolution. For example, a study comparing cranial morphology with respect to changes in brain size, chondrocranial length, and overall cranial size concluded that the structure of cranial variation as a result of these factors was similar in both mice and humans, pointing to similar developmental processes (Martínez-Abadías, Mitteroecker, et al., 2012). Additionally, carefully annotated data pertaining to similarities in the neurodevelopmental sequence of events and patterns of brain enlargement across mammalian orders reveal a high degree of conservation (Clancy, Darlington, & Finlay, 2001; Finlay & Darlington, 1995; Workman, Charvet, Clancy, Darlington, & Finlay, 2013), providing further support for the use of mouse models in the study of human encephalization.

One way to gain further understanding of a complex biological system is to break it using an experimental design that disrupts morphogenesis. In laboratory mice, this is commonly done by disrupting the function of a gene. Studies of mouse models carrying mutations that are proposed to disproportionately affect a particular skull module have demonstrated the structured nature of cranial integration and covariation. Mice carrying mutations that contribute to shorter and wider cranial bases also exhibit wider faces and cranial vaults, while mice carrying mutations causative for a shorter face phenotype also have shorter cranial bases (Hallgrímsson et al., 2007). Additional mouse models have provided support for the spatial packing hypothesis, revealing a significant correlation between increasing basicranial flexion and cranial capacity relative to overall neurocranial size (Hallgrímsson et al., 2007; Lieberman et al., 2008). Mouse models with increased endocranial volumes relative to the cranial base have also

shown interesting relationships with cranial base flexion, quantity of ossified cranial bone, and neurocranial globularity (Lieberman et al., 2008; López et al., 2008).

While these studies have provided an excellent glimpse into the potential relationship between encephalization and skull growth and development, there are aspects of each of these mouse models that limit their relevance to human evolutionary questions. Hypotheses regarding human evolutionary encephalization propose that cranial morphology changed in response to an enlarging brain (Bastir, Rosas, Stringer, et al., 2010; Bruner, 2004, 2007; Lieberman, 2011; Lieberman et al., 2004, 2002; Martínez-Abadías, Esparza, et al., 2012; Weidenreich, 1941). Mouse models with mutations that directly affect basicranial growth and morphology (e.g., *Brachymorph* [bm] and *Pten* mice) (Hallgrímsson et al., 2007; Hallgrímsson & Lieberman, 2008; Lieberman et al., 2008) may reveal correlations of these cranial features with altered brain size or morphology but are based on an experimental model designed to answer the reverse question: whether primary changes in cranial growth or morphology can affect brain size. In order to test the fundamental evolutionary hypothesis, one must adopt a system that is designed to answer the question of whether primary changes in brain size are the stimulus for changes in skull morphology.

Mutations whose primary effect is to directly increase relative brain size provide a more direct test of human encephalization hypotheses. However, certain models, like the megencephaly (*mceph*) model, do not manifest an enlarged brain phenotype until several weeks into postnatal growth (Hallgrímsson et al., 2007), well after the critical time period of cranial ossification and skull growth. The mutation in transgenic mice carrying an altered β-catenin allele effectively restricts expression of the transgene to neural precursors; however, the drastic enlargement of the ventricular system and failure of these mice to reliably survive past birth weaken the impact of any generalizations that might apply to human encephalization (Chenn & Walsh, 2003; López et al., 2008).

Complete knock-out (KO) mouse models, wherein a gene is knocked-out ubiquitously so that it cannot function in any tissue, provide significant experimental insights. However, the fact that many of the gene regulatory networks operating during early development are common to brain and skull morphogenesis complicates the use of KO models in the study of brain and skull interaction. For example, complete KO of a gene known to directly affect brain size cannot be used to study whether a larger brain causes change in skull morphology, as the direct contribution of that gene to the development of other tissues, including bone, has also been canceled in a KO model.

One example of a genetic network that simultaneously affects both brain and bone development is the group of fibroblast growth factors (FGFs) and their associated receptors (FGFRs) (Ornitz & Marie, 2002; Su, Jin, & Chen, 2014), but there are many more (e.g., Richtsmeier & Flaherty, 2013). The importance of the FGF/FGFR network in skeletal development is evidenced by the severe skeletal phenotypic dysmorphologies that can arise in many FGFR-related human skeletal dysplasias, including achondroplasia and craniosynostosis syndromes. In a number of craniosynostosis syndromes, FGFR point mutations can result in a broad range of cranial skeletal phenotypes, including prematurely fused sutures. However, brain anomalies can also occur in these patients (Camfield, Camfield, & Cohen Jr., 2000), and FGFs/FGFRs have been implicated in brain development, contributing to early neurogenesis, glial differentiation, synapse formation, and cerebral cortex size (Ford-Perriss, Abud, & Murphy, 2001; Ozawa, Uruno, Miyakawa, Seo, & Imamura, 1996; Vaccarino et al., 1999).

TABLE 2 Selected examples of cre-recombinase mouse models useful for investigating brain growth and development

Model	Target tissue	Citation
Emx1Cre	Cortex and hippocampus	(Gorski et al., 2002)
Nestin-Cre	Central and peripheral nervous system	(Yaworsky & Kappen, 1999)
Foxg1-Cre	Telencephalon	(Hébert & McConnell, 2000)
Gad2-Cre	Cortex and cerebellum	(Taniguchi et al., 2011)
Scnn1a-Tg3-Cre	Cortex, thalamus, midbrain, cerebellum	(Madisen et al., 2010)
Camk2a-CreERT2	Cortex, hippocampus, striatum	(Madisen et al., 2010)
Thy1-Cre	Postnatal cortex, hippocampus	(Dewachter et al., 2002)

Studies have demonstrated that FGF2 null-mutant mice have smaller cerebral cortices (Vaccarino et al., 1999). However, without knowledge of the direct effect of FGF2 on bone development, any observed changes in skull morphology of FGF2 null-mutant mice could not be attributed to the observed change in brain size. A proper correction for that effect cannot be done statistically because we do not yet fully understand the process. Without detailed knowledge of the basis for the observed changes, we cannot know whether an observed change in skull development was caused (a) directly by the same genetic variant that altered brain morphogenesis, or (b) indirectly as a secondary effect of the change in brain morphogenesis.

Thus, while a number of mouse models have been developed that target genes associated with changes in brain size and brain development (Table 1), caution must be used in interpreting any morphological consequences in the skull, as that genetic change can have a direct effect on bone development. This requires that interested investigators expend significant energy conducting rigorous studies of gene expression during development to better understand the influence of the proposed genetic variant on all developing tissues so that their usefulness in understanding the impact of encephalization on skull morphology is validated and reproducible.

Cre-recombinase technology provides one solution. This technology utilizes bacteriophage Cre-recombinase, an enzyme that will cause recombination between two specific target site nucleotide sequences, known as *loxP* sites (Doyle et al., 2012; Nagy, 2000). In its most simple form, inserting a *loxP* site on either side of a target gene will cause the Cre-recombinase to recognize the *loxP* sites enabling creation of a transgene through deletion, insertion, translocation, or inversion at the targeted DNA site. Recent advancement of this site-specific recombinase technology enables specific cell types or developmental time points to be precisely targeted or a specific external stimulus to act as a trigger for the Cre-recombinase activity. Though some Cre lines have been found to not always behave as expected

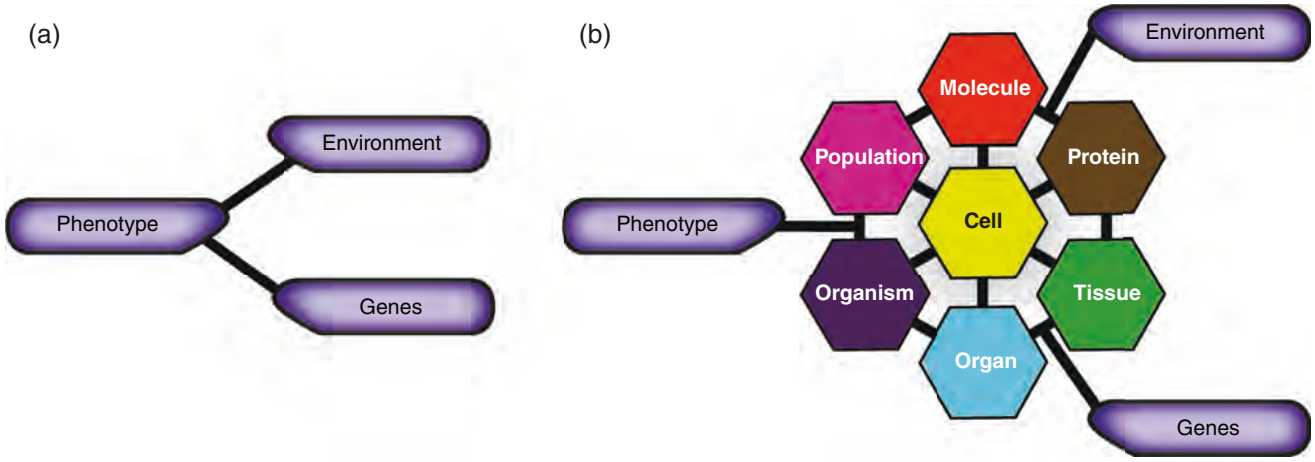

FIGURE 7 (a) It is commonly accepted that environmental and genetic influences contribute to the production of phenotypic variation. (b) A developmental perspective accepts the production of phenotypic variation as a higher order *emergent* result of genetic and environmental influences. These influences provide information that is used by cells to modify developmental pathways that affect phenotypes and life-history traits resulting in changes in our interaction with the environment, including human society. To make sense of these complex relationships, anthropologists must continue to use technologies from other disciplines and expand their collaborative efforts, forming research teams that focus on all hierarchical levels, from the molecule to populations

(see, e.g., Davey et al., 2012; Matthaei, 2007; Schmidt-Supprian & Rajewsky, 2007; Smith, 2011; Song & Palmiter, 2018), tissue- and cell-specific Cre-recombinase lines offer the potential to control the expression pattern of any transgene in anatomical space and/or developmental time. Many cre drivers that target aspects of neurogenesis are available (Table 2).

Skull development occurs through the interaction of genetic networks and mechanical forces of brain expansion, but the skull also influences the directions of brain growth. As noted previously, the development of neural and skeletal tissue is controlled by many of the same genetic networks (Richtsmeier & Flaherty, 2013), and much of evolution occurs by adjustments in developmental programs. Consequently, evolutionary changes in development that arise from modifications in the operation of regulatory hierarchies may affect brain and skull developmental patterns simultaneously—sometimes favorably as in the case of encephalization, and sometimes adversely as in the case of craniofacial disease. Because current anthropological hypotheses regarding encephalization posit that the brain directs changes in skull morphology, and embryonic neural and skeletal tissues respond to similar molecular cues, a test of the spatial packing hypothesis would require an experimental model in which one tissue can be modulated independently to determine the response of the other tissue.

To test the hypothesis that human encephalization is responsible for changes in skull morphology, experimental studies would ideally utilize a mouse model that mimics a mechanism believed to have played a role in human brain evolution. Such an experimental model would require a system in which a genetic variant: (a) affects only neural tissue; (b) is active from the onset of neurogenesis, both prior to the initiation and throughout the duration of cranial bone formation; and (c) does not affect organismal health or viability so that both prenatal and postnatal development may be studied. Such a model would allow tests of the hypothesis that the development of a relatively larger brain contributes to changes in skull development, including the appearance of the human-specific suite of craniofacial characteristics that remain at the forefront of anthropological investigation: a highly flexed cranial base, globular cranial vault, and retracted facial skeleton. Adhering to this type of experimental model has the potential to reveal how change in brain growth dynamics and morphology could affect skull development and eventual morphology.

6 | CONCLUSION

Elucidating the genotype–phenotype transition is a major goal of biology. Though it is commonly said that phenotypic variation is the product of complex interactions between genotype and environment (Figure 7a), mechanisms and processes that integrate genetic instructions and environmental factors to produce organized structure are not well understood. Following others (Carroll, 2008; Hall, 2012), we propose that developmental interactions among factors at all levels contain the information needed to explain the production of phenomes from genomes. Contemporary developmental analyses have focused on genetics to reveal molecular mechanisms underlying phenotypic change but have fallen short in determining how phenotypes are produced because genes do not make structures—developmental processes make structures (Hall, 2012) through the organization and function of cells using instructions provided by genes. How cells utilize those instructions and integrate environmental factors, such as mechanical forces generated by cell proliferation and tissue growth, remains a central question of biology. The process of encephalization evident in the fossil record required changes in neural development. Our biases, as presented in this review, are that (a) answers to questions posed by the skull's apparent adjustment to encephalization require the study of development and (b) changing skull shape, like the changing brain, is a higher order *emergent* result of the hierarchical nature of the genetic, cellular, and biomechanically driven coordination of cells and tissues (Figure 7b).

At this point, it is of value to ask: what is to be gained from understanding how the human skull acquired its modern shape, especially

the characters of increased globularity, flexed cranial base, and retracted facial skeleton? Formation of the brain and skull, and their close developmental and evolutionary relationship, is a complex physical phenomenon. Focus on this challenge will reveal whether primacy of brain *or* skull in head development is a problem of first cause, or whether the answer is more complicated. The process by which the brain has evolved varies across vertebrates, but much is known about the order and process of the evolution of varying neural systems and regions (Borrell & Calegari, 2014; Geschwind & Rakic, 2013; Ghosh & Jessberger, 2013; Striedter, 2005). All regions of the brain did not evolve at the same pace or at the same time, and changes in certain parts of the brain may have affected skull shape while others did not. Our knowledge of the evolution of bone in general and of the vertebrate skull in particular is equally informed (Donoghue & Sansom, 2002; Hall, 2005; Kardong, 2008; Kawasaki & Weiss, 2003; Shimada et al., 2013). Vertebrate evolution reveals a general trend of reduced cranial kinesis through a reduction in the number of bones and the loss or restriction of certain intracranial joints (sutures) over approximately 150 million years of synapsid history that appears to continue through the Cenozoic (Sidor, 2001). Regardless of these dramatic changes in skull morphology, the tight coupling of brain and skull morphology is invariant across vertebrates. Why and how does this occur? Relatively little is known of how the interaction of skeletal and neural tissue might have contributed to their linked evolution, but a study of this relationship is essential for an understanding of the evolution of hominin encephalization.

Knowledge of brain-skull relationships will have meaning beyond knowledge of the evolution of the head. Developmental relationships of brain and skull comprise a complex physical phenomenon that can inform us more generally of the interaction of skeletal tissues and the organs and spaces that they support and protect. Depending upon the approach (computational, experimental, fossil-based), information gained from understanding brain and skull interaction may be generalizable to the development of knowledge pertaining to other complex skeletal-soft tissue systems (e.g., thorax [thoracic viscera & skeleton]; pelvis and perineum [pelvic viscera & skeleton]).

Finally, the evolutionary and developmental relationship between brain and skull can be a source of important clinical information pertaining to many human disorders of the brain and skull. Persistent co-adjustment between brain and skull shape is revealed in the study of craniofacial and neural tube anomalies like anencephaly and holoprosencephaly, and in less life threatening, but similarly devastating, conditions like syndromic craniosynostosis. Understanding the processes that underlie the accommodation of brain and skull in disease involves identification of a series of subtle, though complicated, events occurring in time with cumulative, often worsening effects. Knowledge of these relationships and the potential sequences of developmental events would contribute to patient care by enabling a more accurate prediction of outcomes and informed planning of surgical intervention and/or therapy.

The primacy of either brain or skull in head development represents one of biology's "chicken-and the egg" causality dilemmas. What is clear is that the unique characteristics of the modern human skull (globular cranial vault, highly flexed cranial base, retracted facial skeleton) could only emerge through changes in developmental programs directed by genetic instructions, and that these features, like other evolving phenotypes, are the result of innumerable independent and incremental developmental changes (Carroll, 2003) originating at the level of the cell. Fossil evidence provides a morphological map for generalized changes in the hominin skull that led to the production of a domed cranial vault, a highly flexed cranial base, and a retracted facial skeleton. However, a close look at all the evidence across species and evolutionary time reveals trajectories that are neither direct nor complete. The establishment of these traits and their transmission to the next generation required changes in development directed by instructions given by genes and influenced by the many other factors we have discussed. Genetic mechanisms that propel the appearance of characteristic cranial traits inform developmental programs, but these programs also use environmental inputs like mechanical forces as information, enabling viable responses to perturbations that could disrupt normal development or contribute to the capacity to evolve new forms. Understanding how molecular signaling, cell behavior, and tissue morphogenesis interact with mechanical forces and other environmental inputs in the production of form will provide a means for predicting changing (i.e., evolving, growing, or diseased) phenotypes (Figure 7).

Across evolutionary and developmental time, dynamic changes in brain size and skull shape track one another so that their integration is revealed in two structures that fit soundly, regardless of changes in biomechanical and physiologic functions (Richtsmeier & Flaherty, 2013). As a discipline, we have adequately described the patterns of association between changing brain size and skull morphology as evidenced in the fossil record, and through the study of sister primate groups we have proposed potential processes that account for the patterns that we trace. The challenge for anthropologists is to use the amazing technologies now available in original and collaborative ways to reveal the mechanism(s) underlying the processes we propose to account for the observed patterns.

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