Cerebral blood flow rates in recent great apes are greater than in *Australopithecus* species that had equal or larger brains

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Abstract

Brain metabolic rate is linked mainly to the cost of synaptic activity, so may be a better correlate to cognitive ability in primates than brain size alone. The sizes of arterial foramina in modern and fossil skulls can be used to evaluate blood flow rate, which is proportional to brain metabolic rate. We use this approach to calculate flow rate in the internal carotid arteries ($\dot{Q}_{ICA}$), which supply most of the primate cerebrum. $\dot{Q}_{ICA}$ is up to two times higher in gorillas, chimpanzees and orangutans compared to our australopithecine human relatives, which had equal or larger brains. The scaling relationships between $\dot{Q}_{ICA}$ and brain volume (V_{br}) show exponents of 1.03 across 44 species of living haplorhine primates and 1.41 across 12 species of fossil hominins. Thus the evolutionary trajectory for brain perfusion is much steeper among ancestral hominins than would be predicted from living primates. Between *Ardipithecus* and *Homo sapiens*, V_{br} increased 4.7-fold, but $\dot{Q}_{ICA}$ increased 9.3-fold. In contrast, $\dot{Q}_{ICA}$ is proportional to V_{br} in haplorhine primates. The results suggest that the neurological and cognitive abilities of modern great apes may exceed those of *Australopithecus* species.

Key words: blood flow, brain, cognitive ability, evolution, hominin, primate

1. Introduction

Brain size is the usual measure in discussions of the evolution of cognitive ability among primates, despite recognized shortcomings [1]. Although absolute brain size appears to correlate better with cognitive ability than encephalization quotient, progression index or neocortex ratio [2, 3], an even better correlate might be brain metabolic rate, because it represents the energy cost of neurological function. However, brain metabolic rate is difficult to measure directly in living primates and impossible in extinct ones.

One solution to the problem has been to measure oxygen consumption rates and glucose uptake rates on living mammals in relation to brain size and then apply the results to brain sizes of living and extinct primates. Because physiological rates rarely relate linearly to volumes or masses of tissues, any comparison requires allometric analysis. For example, brain metabolic rate (MR) can be analysed in relation to endocranial volume (≈ brain volume, V_{br}) with an allometric equation of the form, $MR = aV_{br}^{b}$, where a is the *elevation* (or scaling factor, indicating the height of the curve) and b is the scaling *exponent* (indicating the shape of the curve on arithmetic axes). If b = 1.0, then MR is directly proportional to brain size. If b is less than 1, then MR increases with brain size, but the metabolic intensity per unit volume of neural tissue decreases. If b is greater than 1, the metabolic intensity of neural tissue increases. The exponent for brain MR measured as oxygen consumption and glucose use across several mammal species is approximately 0.86, and the exponent for cortical brain blood flow rate in mammals is between 0.81 and 0.87 [4, 5]. The similarity of the exponents indicates that blood flow rate is a good proxy for brain MR in mammals in general. The exponents

indicate that brain MR and blood flow rate increase with brain size but with decreasing metabolic and perfusion intensities of the neural tissue.

Recent studies show that blood flow rate in the internal carotid artery ($\dot{Q}_{ICA}$) can be calculated from the size of the carotid foramen through which it passes to the brain [6]. The artery occupies the foramen lumen almost entirely [7-9], therefore defining the outer radius of the artery (r_o), from which inner radius (r_i) can be estimated, assuming that arterial wall thickness ($r_o - r_i$) is a constant ratio with lumen radius ($w = (r_o - r_i)/r_i$), according to the Law of Laplace. This ratio is valid for the cephalic circulation, but would be higher in arteries in the lower parts of the body where arterial blood pressure is higher. The hemodynamic equation used to calculate $\dot{Q}_{ICA}$, referred to as the "shear stress equation", was derived from Poiseuille: $\dot{Q} = (\tau \pi r_i^3)/(4 \eta)$, where $\dot{Q}$ is blood flow rate ($cm^3 s^{-1}$), τ is wall shear stress (dyne cm^{-2}), r_i is arterial lumen radius (cm) and η is blood viscosity (dyne s cm^{-2}) [10]. The technique was validated in mice, rats and humans, but was initially criticized [11], rebutted [12] and subsequently accepted [13]. However, the calculations involved three questionable assumptions: flow in the cephalic arteries conforms to Poiseuille flow theory, arterial wall shear stress can be calculated accurately from body mass (although there is no functional relationship between them), and the arterial wall thickness-to-lumen radius ratio (w) was a certain constant derived from only two values in the literature.

We have now made significant advancements to the initial methodology by replacing the shear stress equation, and its assumptions, with a new equation derived empirically from a meta-analysis of $\dot{Q}$ versus r_i in 30 studies of seven cephalic arteries of six mammalian genera, arriving at an allometric, so-called "empirical equation", $\dot{Q} = 155\ r_i^{2.49}$ ($R^2 = 0.94$) [14]. In doing so, the tenuous estimation of arterial wall shear stress from body mass is no longer necessary. We have also improved the calculation with a more extensive re-evaluation of carotid arterial wall thickness from 14 studies. The present investigation implements these recent methodological advancements and re-evaluates the scaling of $\dot{Q}_{ICA}$ as a function of V_{br} in extant haplorhine primates and in fossil hominins. The point of our study is to clarify these relationships between *Homo sapiens*, *Australopithecus* and modern great apes (*Pongo, Pan, Gorilla*) to resolve an apparent allometric conflict between our previous studies: One analysis based on 34 species of recent Haplorhini, including *H. sapiens*, resulted in the equation, $\dot{Q}_{ICA} = 8.82 \times 10^{-3}\ V_{br}^{0.95}$ [6], while another analysis of 11 species of fossil hominin, also including *H. sapiens*, produced the equation, $\dot{Q}_{ICA} = 1.70 \times 10^{-4}\ V_{br}^{1.45}$ [15]. Humans are on both analyses with the largest brains, but the exponents of these equations are markedly different, and the lines converge. The present study confirms that hominin ancestors had lower $\dot{Q}_{ICA}$ than predicted from V_{br} with the haplorhine equation. $\dot{Q}_{ICA}$ in modern great apes is about twice that in *Australopithecus* species, despite similar or smaller V_{br}.

2. Results

(a) ICA blood flow rate in great apes and *Australopithecus*

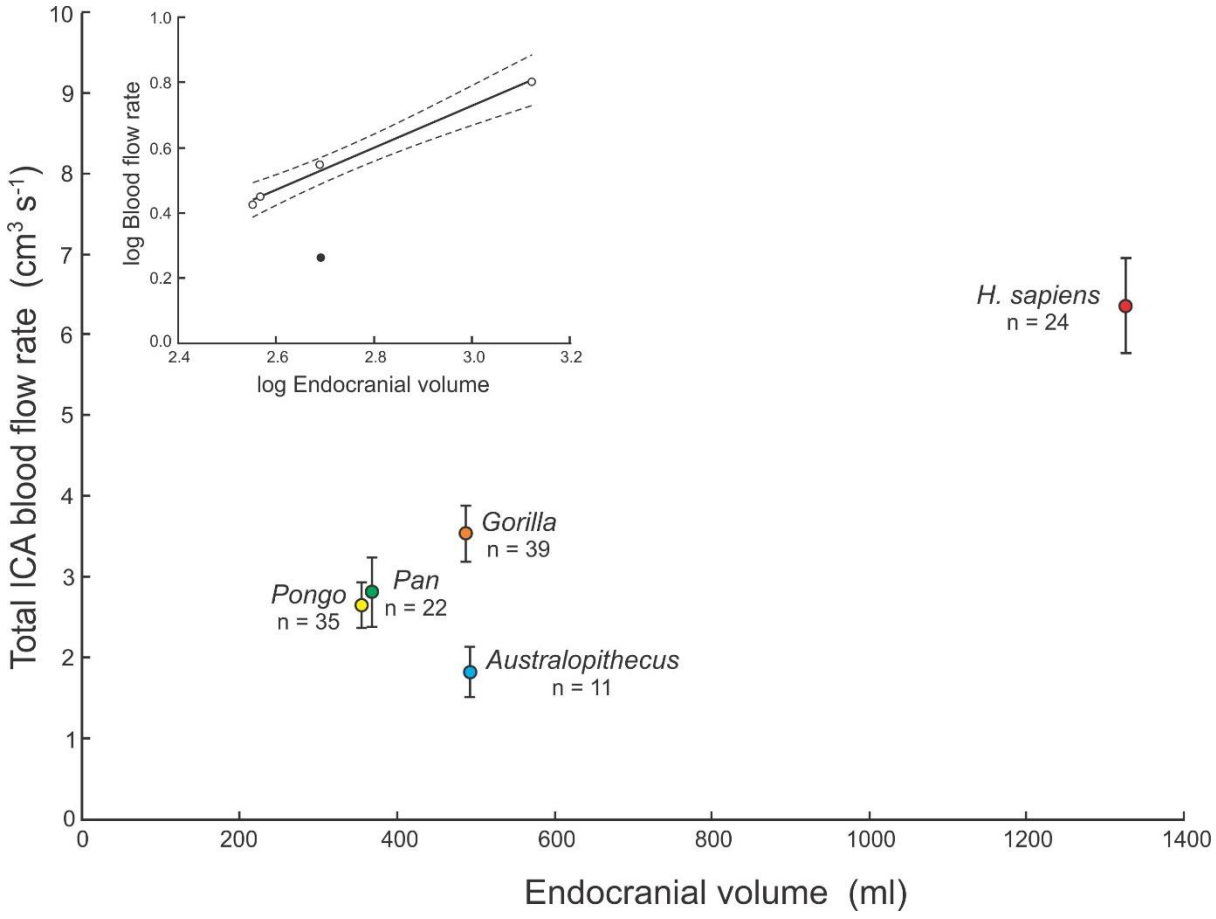

Figure 1. Total blood flow rate of both ICAs ($\dot{Q}_{ICA}$), calculated with the new, "empirical equation" and a wall thickness-to-lumen radius ratio of w = 0.30, in relation to endocranial volume (V_{br}). Means, 95% confidence intervals, and sample sizes are shown. Inset is the regression of $\log_{10}$-$\dot{Q}_{ICA}$ against $\log_{10}$-V_{br} for four genera of hominids, namely *Pongo*, *Pan*, *Gorilla* and archaic *H. sapiens* (unfilled circles), showing that *Australopithecus* (filled circle) falls below the regression mean's 95% CI bands. Statistics for individual species are in Table S2.

Table 1. Results of ANOVA ($F_{4, 126} = 43$, $P < 0.0001$) and Tukey's post hoc test comparing differences in total blood flow rate of both internal carotid arteries ($\dot{Q}_{ICA}$) in four genera of hominids. P values less than or equal to 0.05 indicate a statistically significant difference.

	Pongo	*Pan*	*Homo*	*Australopithecus*
Gorilla	0.0012	0.036	<0.0001	<0.0001
Pongo		0.98 (NS)	<0.0001	0.0123
Pan			<0.0001	0.0066
Homo				<0.0001

Because two ICAs enter the brain, all reported values of $\dot{Q}_{ICA}$ are the sum of right and left ICA foramina or twice the value calculated from one intact foramen in fossil skulls. $\dot{Q}_{ICA}$ in relation to V_{br} in recent *Pongo*, *Pan*, *Gorilla* and *Homo* and in fossil *Australopithecus* reveal significant differences (Fig. 1; See Table S2 for individual species data). ANOVA and Tukey's multiple comparisons test distinguish all five genera from one another, except between *Pongo* and *Pan* (Table 1). $\dot{Q}_{ICA}$ in *Australopithecus* was the lowest of all genera and it sits below the 95% confidence belt for a linear regression of $\log_{10}$-Q_{ICA} data on $\log_{10}$-V_{br} for the living genera (Fig. 1 inset). Thus, $\dot{Q}_{ICA}$ is significantly higher in all genera of modern great apes compared to *Australopithecus* despite equal or smaller V_{br}.

(b) ICA blood flow rate in fossil hominins and extant haplorhine primates

Carotid foramen radius (r_o, cm) and endocranial volume (V_{br}, ml) in fossil hominin skulls, including *Ardipithecus ramidus*, produce the regression $r_o = 0.0048\ V_{br}^{0.57\pm0.12\ CI}$ ($R^2 = 0.91$). New values of $\dot{Q}_{ICA}$ calculated with the "empirical equation" and w = 0.30 in 44 species of haplorhine primates and 12 species of fossil hominins are compared in Fig. 2 (Table S3). The regressions are $\dot{Q}_{ICA} = 0.0068\ V_{br}^{1.03\pm0.07\ CI}$ ($R^2 = 0.95$) for haplorhines and $\dot{Q}_{ICA} = 0.00028\ V_{br}^{1.41\pm0.30\ CI}$ ($R^2 = 0.91$) for hominins. The two exponents are significantly different ($F_{1, 53} = 6.27$; $P = 0.015$), and there is no overlap of the data (Johnson-Neyman test showed significant differences in the data below V_{br} = 1708 ml). The exponent for haplorhines is not significantly different from 1.0, meaning that $\dot{Q}_{ICA}$ is proportional to V_{br}. In contrast, the extremely high exponent for hominins shows that V_{br} increased 4.7-fold, and $\dot{Q}_{ICA}$ increased 9.3-fold, between *Ardipithecus* and *Homo sapiens*, revealing a 2-fold increase in volume-specific perfusion rate.

Recent analyses of primate regional brain anatomy, including the volumes of neocortical grey matter (V_{grey}) and telencephalon (V_{tele}) are now available [16-18] (Table S4). These data include 17 species of haplorhine primates for which we have ICA foramen radius [6, 13]. Assuming w = 0.30 and using the empirical equation, we find $\dot{Q}_{ICA} = 0.0135\ V_{grey}^{\ 1.06\pm0.14\ CI}$ ($R^2 = 0.95$) (Fig. 3A) and $\dot{Q}_{ICA} = 0.0103\ V_{tele}^{\ 1.01\pm0.12\ CI}$ ($R^2 = 0.96$) (Fig. 3B). Both exponents are not significantly different from 1.0. We also have ICA foramen sizes for 26 species of haplorhine primates and 15 species of strepsirrhine primates in which total neocortex volume (V_{neo}), including white and grey matter, has been measured [19, 20] (Table S5). The regressions for these species are $\dot{Q}_{ICA} = 0.0062\ V_{neo}^{\ 1.12\pm0.15\ CI}$ ($R^2 = 0.91$) for haplorhines and $\dot{Q}_{ICA} = 0.0012\ V_{neo}^{\ 0.96\pm0.42\ CI}$ ($R^2 = 0.66$) for strepsirrhines (Fig. S1). The regression for strepsirrhines is not particularly tight, so the exponent is not significantly different from the haplorhines ($F_{1, 37} = 0.692$; $P = 0.41$), but the elevation is significantly lower in strepsirrhines ($F_{1, 38} = 74.18$; $P < 0.0001$). Strepsirrhine primates have reduced ICA and a different pattern of brain perfusion [21], which explains low $\dot{Q}_{ICA}$ found in this and previous studies [6]. Therefore here we consider only haplorhines in which only the internal carotid and vertebral arteries supply the brain. The scaling of ICA blood flow rate in haplorhine primates in relation to different measures of total or partial brain volumes show exponents not significantly different from 1.0, but significantly higher than 0.86, the exponent apparent in mammals in general.

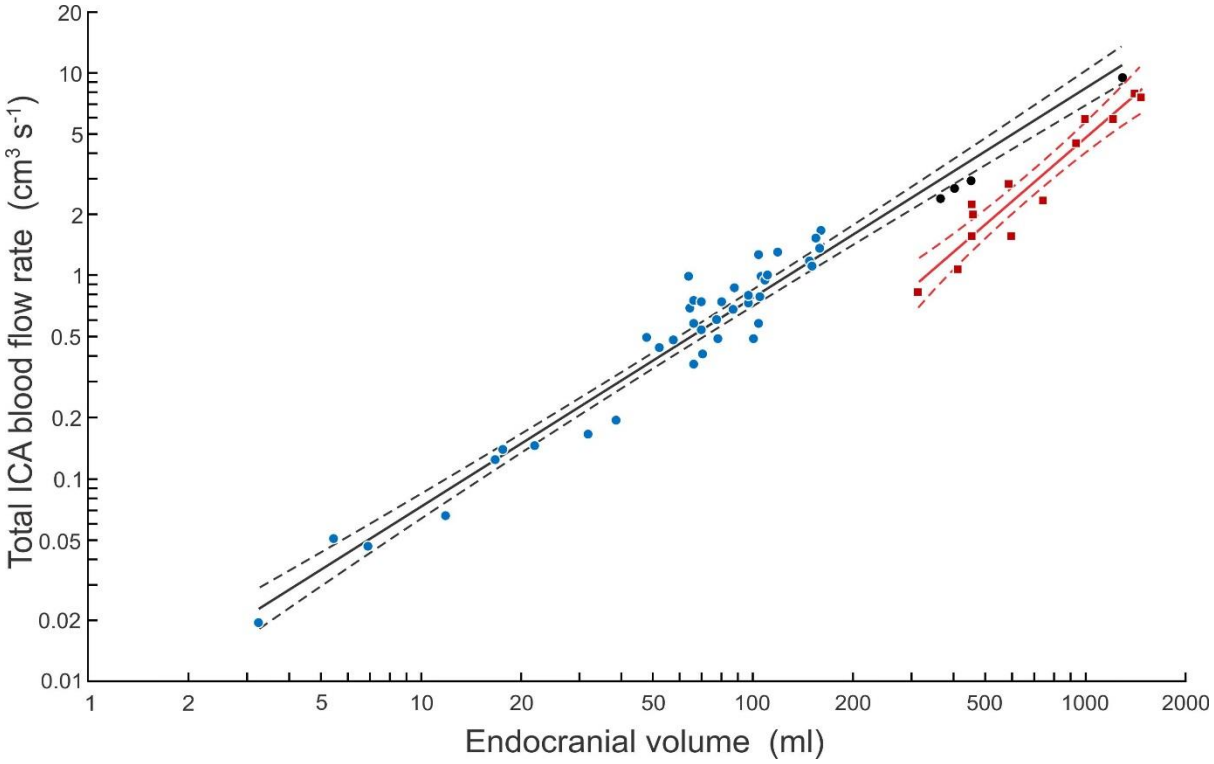

Figure 2. Total blood flow rate of both ICAs ($\dot{Q}_{ICA}$) in relation to endocranial volume (V_{br}). $\dot{Q}_{ICA}$ is calculated with the "empirical equation" and a wall thickness-to-lumen radius ratio of w = 0.30 from ICA foramen radius data. The equation for 44 species of haplorhine primates (blue and black circles) is $\dot{Q}_{ICA} = 0.0068\ V_{br}^{\ 1.03\pm0.07\ CI}$ ($R^2 = 0.95$), and that for 12 species of hominins is $\dot{Q}_{ICA} = 0.00028\ V_{br}^{1.41\pm0.30\ CI}$ ($R^2 = 0.91$). Solid lines are the regression mean, dashed lines represent the 95% confidence bands. Black circles are *Pongo, Pan, Gorilla* and *Homo sapiens*. See Table S3 for individual data derived from Seymour et al. (2015), Boyer and Harrington (2019) and Seymour et al. (2017).

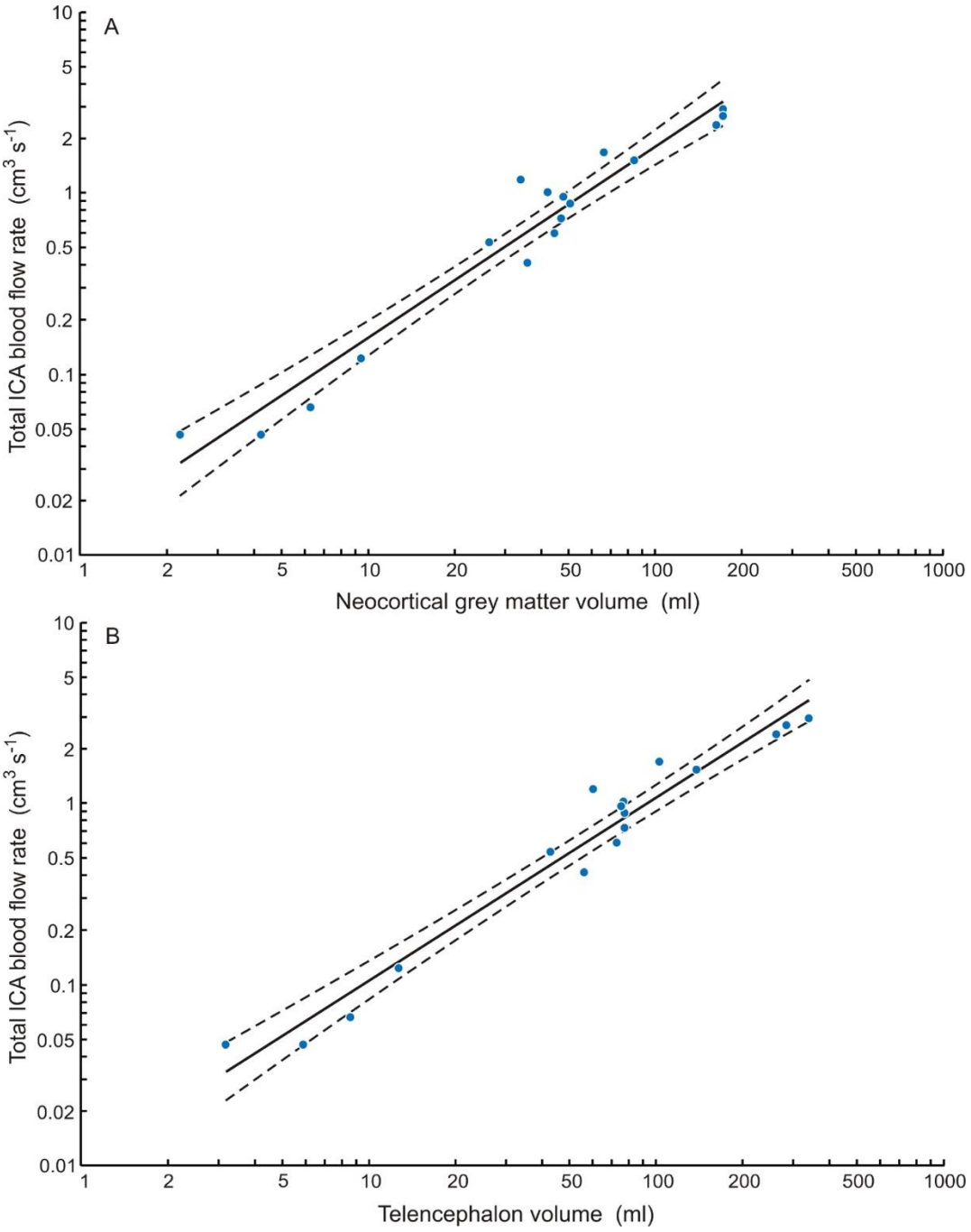

Figure 3. Total blood flow rate of both ICAs ($\dot{Q}_{ICA}$) in relation to (A) neocortical grey matter volume (V_{neo}) and (B) telencephalon volume (V_{tele})in 17 species of haplorhine primates $\dot{Q}_{ICA}$ values calculated with the "empirical equation" and w = 0.30 from ICA foramen sizes in Seymour et al. (2015) and Boyer and Harrison (2019). Volume data are from Navarrete et al (2018), which include data from Stephan et al. (1981) and Zilles and Rehkämper (1988); duplicate or triplicate data were averaged to obtain one point for each species. The equations are, $\dot{Q}_{ICA} = 0.0135\ V_{neo}^{1.06\pm0.14\ CI}$ ($R^2 = 0.95$) and $\dot{Q}_{ICA} = 0.0103\ V_{tele}^{1.01\pm0.12\ CI}$ ($R^2 = 0.96$). Solid line is the regression mean, dashed lines represent the 95% confidence bands. See Table S4 for individual data.

3. Discussion

The present study indicates that the non-human modern great apes have a significantly greater cerebral blood flow, and by inference metabolic demand, than ancestral *Australopithecus* (Fig. 1). Although *Gorilla* has V_{br} values similar to *Australopithecus*, *Gorilla* $\dot{Q}_{ICA}$ is approximately twice as high. *Pongo* and *Pan* have smaller V_{br} than *Australopithecus*, but significantly higher $\dot{Q}_{ICA}$. The difference is also apparent in $\dot{Q}_{ICA}$ scaling of extant haplorhine primates and fossil hominins (Fig. 2), where the great apes (black points) are higher than those for hominins. The implication of these disparate results is that the position of the human brain appears to be an isometric ("a scaled up") version of a haplorhine primate brain, something noticed previously [22-24], but the trajectory of its evolution among hominins is quite hyperallometric.

The analysis of $\dot{Q}_{ICA}$ against V_{br} with the new approach produces exponents of 1.03 in extant haplorhines and 1.41 in fossil hominins (Fig. 2). The hominin exponent is similar to 1.45 calculated formerly from the shear stress equation [15]. The major determinate of $\dot{Q}_{ICA}$ is the extremely high allometric exponent of ICA foramen radius, which scales with $V_{br}^{0.57}$. If the skull increased in size while maintaining the same shape (isometric scaling), ICA radius would scale with $V_{br}^{0.33}$. If brain perfusion is assumed to scale with negative allometry (e.g. $V_{br}^{0.86}$), then foramen radius would scale with an exponent even less than 0.33. Therefore, the high exponent for hominin ICA foramen radius can mean nothing but an extraordinary increase in brain perfusion by the ICAs. The 1.41 exponent for $\dot{Q}_{ICA}$ is so high that it cannot be compensated by flow in the vertebral arteries to achieve even isometric total brain perfusion in hominins. (See the Supplementary Material for an analysis of the roles of the vertebral arteries in hominins and haplorhines.)

The $\dot{Q}_{ICA}$ exponents in haplorhines are also high, near 1.0 in relation to total brain volume (Fig. 2), neocortical grey matter volume (Fig. 3A), telencephalon volume (Fig. 3B) and neocortex volume (Fig. S1). The exponents are all statistically significantly higher than 0.86 expected for $\dot{Q}_{TOTAL}$ in mammals in general. The difference between exponents of 1.0 and 0.86 is not trivial. Over the range of V_{br} of the haplorhines, volume-specific $\dot{Q}_{ICA}$ does not change at all with an exponent of 1.0, but drops to 50% with an exponent of 0.86. If we assume that the extant haplorhines assessed in this study represent the conditions of their ancestors, we see an increase in brain size and complexity across evolutionary time. The Haplorhini split from the Strepsirrhini about 66-69 Mya; within the Haplorhini, the Platyrrhini (New World monkeys) split from the Catarrhini (Old World monkeys and apes) about 46 Mya, and, within the Catarrhini, the Hominoidea (apes) arose about 32 Mya [25]. Thus the small-brained platyrrhines are the oldest, and larger-brained hominoids are the youngest groups of haplorhines. Our original phylogenetically-informed analysis indicated that the younger groups evolved a progressively higher than expected rate of brain perfusion, supplying mainly the cerebral cortex [6]. As brain volume increased, the relative proportion of the whole cerebrum and the level of cortical folding have increased faster. Haplorhine $\dot{Q}_{ICA}$ increases steeply with neocortical grey matter and telencephalon volumes (Fig. 3) and with neocortex volume (Fig.

S1). Most of the volume increase of the cerebral cortex is due to an increase in the communication network (white matter) rather than the cognitive tissue, rich in synapses (grey matter). In haplorhine primates, the volume of grey matter increases with total brain volume to the 0.985 power (nearly linearly proportional), but white matter increases with the 1.241 power [26]. Our analysis shows that $\dot{Q}_{ICA}$ scales with $V_{br}^{1.03}$ (Fig. 2), corresponding well to the scaling of neocortical grey matter but not white matter. This seems reasonable because grey matter is about 2-4 times more active metabolically than white matter [27, 28], and thus has greater influence on the scaling of $\dot{Q}_{ICA}$ against V_{br}.

(a) Implications

The results cast doubt over the notion that the neurological and cognitive traits of modern great apes adequately represent the abilities of *Australopithecus* species. The use of modern primates as a proxy for hominin evolution may have prevailed historically due to similar brain sizes, with the great apes between 300 – 500 ml, compared to 315 ml in *Ardipithecus* [29], and 475-500 ml in *Australopithecus* (Table S2). The fact that $\dot{Q}_{ICA}$ is up to 2-fold higher in *Gorilla* than in *Australopithecus* is surprising given that the australopithecines have been placed between great apes and humans on the basis of several measures relating to brain and intelligence [30, 31]. Perhaps underlying assumptions that cognitive ability, brain metabolic rate and blood flow rate all scale with brain size in parallel, and that the patterns evident in living haplorhine primates apply to hominins, are incorrect. Indeed, this study shows that the scaling of $\dot{Q}_{ICA}$ follows quite different trajectories in haplorhines and hominins, indicating that hominins started with low $\dot{Q}_{ICA}$ in *Ardipithecus* 4.4 million years ago [32], but ended up very high in modern humans. Because the chimpanzee and human lineages diverged about 6 – 7.5 million years ago [25, 33, 34], it is apparent that the ancestors of great apes experienced appreciable cognitive development during their evolution. In addition to a general increase in brain size and body size of great apes within the Haplorhini, the data indicate an increasing metabolic intensity of cerebral brain tissue, because $\dot{Q}_{ICA}$ increases with volumes of the cognitive parts of the brain with exponents near 1.0 (Figs. 2, 3), rather than 0.86 that is accepted for mammalian brains. The progression of increasing perfusion matches the evolutionary order of 'information processing capacity' among haplorhines as indicated not only from anatomy and physiology (e.g., number of neurons, degree of connectivity, axonal conduction velocity), but also from behavioral measures (e.g., capacity of memory, mental manipulation, social interactions, etc.) [31, 35].

Because the ICA supplies almost all of the cerebrum in humans, we assume that, in addition to increasing brain size, the rise in volume-specific $\dot{Q}_{ICA}$ in the hominins traces a rapid evolutionary rise in the metabolic intensity of the cerebral tissue. This would correlate with an increase in cognitive ability from *Australopithecus*, as the early representatives of hominin evolution, to modern *Homo sapiens,* that exceeded that determined by brain volume alone. Such development is not

inevitable, however, as evidenced by similar values of $\dot{Q}_{ICA}$ and V_{br} in *H. naledi* and *H. floresiensis* as in *Australopithecus* species, despite approximately 2.5 million years between them [36, 37]. It is thought that *H. naledi* and *H. floresiensis* branched from ancient small-brained *Homo* ancestors, possibly independently [34, 38, 39]. These two recent species raise problems in relating cognitive ability to measures of brain perfusion rate as well as brain size [30].

The high cerebral perfusion may relate to modern great apes living in social family groups that require complex understanding of family interrelationship and hierarchies [40]. Such family structures demand a higher degree of cognitive capacity to partake in social behaviours that would render individuals fit for mating and territory defence, in comparison to solitary mammals [41, 42]. Such social drivers for cognitive evolution are often attributed to *Australopithecus* and early *Homo*. However, the presumption that the same predecessor of great apes and humans did not exhibit as complex family cooperation as modern great apes would suggest that great apes evolved this life history trait in parallel with hominins. This would have contributed to increases in ancestral great ape cerebral metabolic and ICA blood flow rates, in a similar way to the *Homo* predecessors. It can be argued that the cognitive capacity that favoured the survival of the genus *Homo* equally facilitated the survival of ancestral great apes. The requirement for cerebral specialisation may have ultimately contributed to modern great apes being more cognitively advanced than *Australopithecus*.

2. Methods

New measurements were made from 82 skulls from six species of great apes in museum collections (See Supplementary Material for specimen data). Endocranial volume (V_{br}; ml) was measured by sealing large foramina in the skull with cotton wool and filling the brain case with rice or plastic beads to the level of the foramen magnum, gently agitating to achieve uniform compaction, and then emptying into a graduated cylinder and recording the compacted volume. Because the carotid artery occupies the foramen lumen almost entirely, the outer radius of the artery is defined by the radius of the foramen (r_o; cm). Thus, the radii of the left and right carotid foramina were measured from photographs, captured orthogonal to the opening, together with a 0.5-mm graduated scale, positioned at the level of the opening. An ellipse was fitted to the inside of the foramen opening with imageJ (Open Source, imagej.net), and r_o was taken as the radius of a perfect circle with the measured elliptical area.

The literature was searched for data on lumen radius (r_i, cm) and wall thickness of normally pressurized internal carotid and common carotid arteries. Wall thickness was taken as the difference between outer radius (r_o) and lumen radius (r_i) and was expressed as the ratio, $w = (r_o - r_i)/r_i$. The mean value of w was 0.30, which was used in the calculations (See Supplementary Material and Table S1 for data).

Blood flow rate in the ICA was calculated from carotid foramen radius (r_o) using the "empirical equation" ($\dot{Q}_{ICA} = 155\ r_i^{2.49}$) and calculated lumen radius, $r_i = r_o /(1+w)$. The results of this approach are slightly better statistically, but are similar to those from the Poiseuille shear stress equation used previously (See Supplementary Material for detailed comparison of computational approaches and their results).

The new calculations were applied to r_o and V_{br} data from previous studies of 44 species of haplorhine primates [6, 13], and 12 species of hominin (two points for early and late *Homo erectus*), including 8 specimens attributed to *Australopithecus africanus* and 3 attributed to *A. afarensis* [24]. A new hominin ICA foramen radius point for *Ardipithecus ramidus* was obtained by measuring three scaled figures of the basal skull and taking the mean V_{br} from the publications [29, 43]. In addition, $\dot{Q}_{ICA}$ was compared allometrically to the volumes of telencephalon, neocortex and neocortical grey matter from recent publications [16-18].

Data are presented as means with 95% confidence intervals (CI). Allometric data were $\log_{10}$-transformed prior to fitting ordinary least-squares linear regressions [44, 45] and performing ANCOVA to test for significant differences in scaling exponents and elevations [46]. If the exponents differed significantly, differences in the elevation cannot be evaluated, so the Johnson-Neyman technique revealed the region in which data from individual species were significantly different [47]. Statistics on mean data also included ANOVA and Tukey's multiple comparisons test.

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Author contributions

Conceptualization: R.S.S.; Data gathering: R.S.S., V.B, E.P.S, Q.H., T.J.N., B.Z., C.M.; Formal analysis: R.S.S., Q.H., V.B., E.P.S.; Writing - original draft: R.S.S., V.B.; Writing - review and editing: R.S.S., E.P.S., Q.H., T.J.N., B.Z., C.M.; Project administration: R.S.S.

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