THE ROYAL SOCIETY PUBLISHING

PROCEEDINGS B

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

Roger S. Seymour, Vanya Bosiocic, Edward P. Snelling, Prince C. Chikezie, Qiaohui Hu, Thomas J. Nelson, Bernhard Zipfel and Case V. Miller

Article citation details
Proc. R. Soc. B **286**: 20192208.
http://dx.doi.org/10.1098/rspb.2019.2208

Review timeline

Original submission:	19 June 2019
1st revised submission:	14 August 2019
2nd revised submission:	22 September 2019
3rd revised submission:	21 October 2019
Final acceptance:	21 October 2019

Note: Reports are unedited and appear as submitted by the referee. The review history appears in chronological order.

Review History

RSPB-2019-1443.R0 (Original submission)

Review form: Reviewer 1

Recommendation
Major revision is needed (please make suggestions in comments)

Scientific importance: Is the manuscript an original and important contribution to its field?
Good

General interest: Is the paper of sufficient general interest?
Excellent

Quality of the paper: Is the overall quality of the paper suitable?
Acceptable

Is the length of the paper justified?
Yes

Should the paper be seen by a specialist statistical reviewer?
No

Do you have any concerns about statistical analyses in this paper? If so, please specify them explicitly in your report.
No

It is a condition of publication that authors make their supporting data, code and materials available - either as supplementary material or hosted in an external repository. Please rate, if applicable, the supporting data on the following criteria.

Is it accessible?
Yes

Is it clear?
Yes

Is it adequate?
Yes

Do you have any ethical concerns with this paper?
No

Comments to the Author
Seymore et al. present a novel analysis of the relationship between perfusion rate through the internal carotid arteries and brain size, as measured by endocranial volume, in primates with a particular focus upon hominins as compared to the other great apes. The data represent some novel data from nine species of great ape, together with a re-analysis of significant published raw data on a range of haplorhines from multiple sources. The re-analysis method is novel and important as it for the first time uses a recently published empirical data-derived formula to calculate blood flow rate in the internal carotid arteries from raw foramen radius measurements. This empirical approach is applied here to haplorhines and hominins for the first time. Seymore et al. report that extinct hominins comparable in brain size to non-human great apes possess relatively much lower rates of perfusion through the internal carotid artery. They further report that the relative rate of increase in brain perfusion during hominin evolution is significantly different to that observed across the rest of haplorhine primates. This is a novel and interesting finding with potentially wide implications. There are however significant issues with the way that the data are presented and the way that they are interpreted (see below). If these can be addressed, then this work would certainly be of interest to the readership of Proceedings B.

Major revisions

Results

Figure 1 essentially represents a zoom in of the region of figure 2 that corresponds to the top right region of figure 2 that contains the extant great apes and the fossil hominins. Why is Australopithecus the only extinct hominin shown in this figure? Surely the conclusions of the paper relate not only to Australopithecus but also to all of the other extinct hominins with approximately similar ECVs? In the present form, figure 1 appears as a selectively presented subset of figure 2. Given this, it would make much more sense to present the current figure 2 as

the first figure, and an expanded current figure 1 (ie. with all extinct hominins in both the linear and logarithmic plots) as the second figure.

Discussion

Final paragraph: the interpretation that the authors propose is confused. They seem to be suggesting that the different great ape lineages evolved enhanced cognitive ability, and therefore greater QICA relative to brain size, independently of one another and of hominins ie. multiple independent evolution of social groups and enhanced cognitive ability (lines 194-196). It is more parsimonius, and more plausible, to posit that the LCA of the great apes had high relative QICA, and accompanying cognitive and social abilities, as did all subsequent lineages of great apes apart from the human lineage after it split with the chimp-human LCA 6-7.5 mya. Thus, the human lineage took an unusual trajectory after splitting from the chimp lineage.

This interpretation would correlate with evidence for increased expansion of the pre-frontal cortex (and its associations with social/group intelligence) in the ancestor of the great apes (Smaers et al. 2017 Current Biology). A relative decrease in QICA in the human lineage after it diverged from chimps and then a subsequent steeper increase in QICA relative to brain size, the central arguement of this paper (figure 2), would also correlate with the abundant recent evidence for significant genetic and developmental differences that evolved in the human lineage after it separated from the chimp lineage (eg. Dennis et al. 2012 Cell, Charrier et al. 2012 Cell, Florio et al. 2015 Science, Ju et al. 2016 Elife, Fiddes et al. 2018 Cell, Suzuki et al. 2018 Cell, Pollen et al. 2019 Cell) that are also associated with cognition and social behaviour in humans (Doan et al. 2016 Cell).

Minor revisions

Abstract

Line 6: The statement that the ICAs supply 'most of the primate cerebrum' is an oversimplification, since the cerebral arterial blood supply derives from the Circle of Willis, an anastomosis supplied by the ICAs and the basilar artery.

Introduction

33: should read 'glucose use across several mammalian species…'

42-44: The wording here of the comparison between cephalic and lower body circulation ration between arterial wall thickness and lumen radius is confused. The ratio would indeed be higher for lower body circulation, but would be still be constant, and the extension of LaPlace's law is therefore no less valid.

Results

77-79: The data point for Australopithecus does not simply sit below the linear regression intervals for the extant taxa, but is far far below. The text should be altered to add emphasis to this finding.

84: The value of 0.3 for the ratio of the ICA to the carotid foramen is only explained in the legend to figure S4. It should be made clear in the main text how this ratio was derived.

108: a figure is given for the scaling exponent in mammals in general as 0.86, but it should be made clear where this data is derived from ie. with a citation.

Discussion

136-137: Assuming that extant taxa represent conditions of their ancestors is not a sensible assumption, especially in the evolutionary history of the haplorhine cortex. This should be re-phrased so as to be more precise ie. indicating that by inference from the data from extant haplorhines, we see an increase in brain size and complexity across evolutionary time on the human lineage.

141-142: the authors should avoid phrases such as 'are the oldest' in relation to lineages; all lineages are the same age. Rather they should refer to the particular characteristics in question in terms of age eg. the large brains seen in the hominoid lineage have a more recent evolutionary origin than the smaller brains found in extant platyrrhines.

144-145: The authors contend that the level of cortical foliation increased at a faster rate than brain volume. What is this based upon? It is not obvious that any measure of foliation (eg. foliation index) is directly comparable to volume and therefore this statement seems unwarranted.

152-154: Comparing the metabolic activity of grey matter and white matter is something of a false dichotomy, since much of the metabolic activity of projection neurons that supports the axon (white matter) occurs in the cell body (grey matter), but long axons contribute hugely to the metabolic needs of projection neurons. This sentence should be removed.

168-171: The date of the human-chimp LCA does not directly inform the cognitive evolution in the lineage of the LCA of the great apes, since the LCA of great apes lived ~15-20 MYA. This should be re-written.

173: the authors should refrain from referring to 'cognitive' parts of the brain that exclude the cerebellum, and instead refer to the neocortex or telencephalon (as shown in figure 3).

187-188: The final sentence in this paragraph rather undermines the central assumption that underlies the conclusions of the paper, namely that QICA can act as a proxy for cognitive ability. As such, this warrants a more thorough discussion.

Methods

Line204: 9 species of great ape (ie. including hominins) are listed in table S2 as being the source of the novel data, not 6 as is stated in the text.

Supplementary text

Computational approaches to evaluate blood flow rate from foramen size

Paragraph 2: the authors state that 'Central mean arterial blood pressure is practically independent of body mass in mammals the size of primates.' This is a vague statement and should be justified properly.

ICA blood flow calculated with the shear stress and empirical equations

Paragraph 1: The authors contend that the use of w=0.3 in the empirical equation increases the QICA by 25% in hominins, citing figure S2. However, S2 compares QICA to ECV for hominins and does not include data on the mean and standard error of values for QICA as calculated using the different equations.

Paragraph 3: Again, the reference to the 'cognitive parts' of the brain here are not warranted for the same reason as above (Discussion, line 173).

Roles of the ICAs and VAs in total brain perfusion in hominins

Paragraph 1: The authors discuss published and unpublished data suggesting that the majority of cerebral perfusion and flow derives from the ICAs. This is certainly true, but it does not follow that 'the ICAs are relied upon for servicing almost all of the cognitive parts of the human brain. The VAs supply mainly the upper spinal cord, brainstem and cerebellum.' Given the anastomotic relationship between the ICAs, the VAs, and the cerebral circulation, this inference is not warranted. Secondly, given the evidence of recent years (eg Diedrichsen et al. 2019 Neuron), it is not true to imply that the cerebellum is not a 'cognitive' part of the brain. The inference of different cephalic spatial perfusions of ICAs vs VAs should be removed from the text.

Paragraph 2: The explanations behind the authors' inferences of QVA in fossil hominins is not clear. This explanation is aimed at the non-specialist, and so should not assume a working relationship with allometric power equations. In particular, the distinction between factors and terms should be elaborated and made clearer.

Figures

Figure 2

The red dots presumably represent the 12 species of hominins. The figure legend should make this explicit.

Figure S1

Confidence intervals are not reported for these plots. Despite the fact that there is not a significant difference in the exponents between the groups plotted, confidence intervals should nevertheless be shown.

Figure S3 & S4

It should be indicated in the legend which line of correlation line applies to which dataset.

Review form: Reviewer 2

Recommendation
Major revision is needed (please make suggestions in comments)

Scientific importance: Is the manuscript an original and important contribution to its field?
Excellent

General interest: Is the paper of sufficient general interest?
Excellent

Quality of the paper: Is the overall quality of the paper suitable?
Good

Is the length of the paper justified?
Yes

Should the paper be seen by a specialist statistical reviewer?
Yes

Do you have any concerns about statistical analyses in this paper? If so, please specify them explicitly in your report.
No

It is a condition of publication that authors make their supporting data, code and materials available - either as supplementary material or hosted in an external repository. Please rate, if applicable, the supporting data on the following criteria.

Is it accessible?
Yes

Is it clear?
Yes

Is it adequate?
Yes

Do you have any ethical concerns with this paper?
No

Comments to the Author
This is an important and interesting question, harnessing methods that the authors have been instrumental in developing. While I love the premise and approach, I'm having trouble envisioning the evolutionary trajectories that would be necessary to explain the authors' findings and to support their interpretation.

There is a fairly well-defined allometry linking Qica and endocranial volume (defining perfusion) in extant Haplorhine primates. Humans are on that line, as are (although perhaps slightly below, see note below) the other extant great apes. But the fossil hominins are not – they follow their own slope and only converge with the haplorhine line at the upper extreme of cranial capacity represented by modern humans.

If we assume (as the authors reasonably do) that the smaller brained/earlier hominins (australopiths) are likely representative of e.g. the human-pan LCA, this implies that chimps and humans had an ancestor with a cerebral perfusion below that predicted by the more general haplorhine allometry, and that the lineages leading to pan and human then increased blood perfusion in parallel in a fashion that somehow ended up (with humans and living pan species) converging with the extant haplorhine allometry.

How do 44 species of Haplorhine primates, including humans and other extant great apes, end up adhering to a consistent scaling relationship between Qica and cranial volume, while some of the ancestors of a few of those species (humans, and likely, pan) were on a different allometry, with a markedly different slope, until recently? Would it not require the evolution of a derived reduction in cerebral perfusion (implying reduced cognitive abilities for brain and body size than e.g. OWM) specific to early ancestral apes that was reversed in human and pan – and with the latter more recently converging with the haplorhine allometry as a mere coincidence? Is it not

parsimonious to assume that there is something "off" about the hominin allometry reconstructed from fossil specimens? At a minimum, I think this possibility should be entertained. Perhaps I am missing some obvious interpretation, but the pattern of findings that the authors report strikes me as difficult to explain.

The authors grapple with this in the final paragraph:
The high cerebral perfusion may relate to modern great apes living in social family groups
190 that require complex understanding of family interrelationship and hierarchies [40]. Such family
191 structures demand a higher degree of cognitive capacity to partake in social behaviours that would
192 render individuals fit for mating and territory defence, in comparison to solitary mammals [41, 42].

>That is fine – but all extant Haplorhine, not just modern great apes, adhere to a common allometry. This is not acknowledged or discussed, but should be (this is what is most paradoxical and difficult to explain)

193 Such social drivers for cognitive evolution are often attributed to Australopithecus and early Homo.
194 However, the presumption that the same predecessor of great apes and humans did not exhibit as
195 complex family cooperation as modern great apes would suggest that great apes evolved this life
196 history trait in parallel with hominins. This would have contributed to increases in ancestral great
197 ape cerebral metabolic and ICA blood flow rates, in a similar way to the Homo predecessors. It can
198 be argued that the cognitive capacity that favoured the survival of the genus Homo equally
199 facilitated the survival of ancestral great apes. The requirement for cerebral specialisation may have
200 ultimately contributed to modern great apes being more cognitively advanced than
201 Australopithecus.

 Right – but again, these hypothesized derived levels of "high" blood flow that were proposed to evolve in parallel in the various great ape lineages are actually not high but just what would be predicted for haplorhines of their brain size…again, hard to explain this.

Specific points:

The implication of these
117 disparate results is that the position of the human brain appears to be an isometric ("a scaled up")
118 version of a haplorhine primate brain, something noticed previously [22-24], but the trajectory of its
119 evolution among hominins is quite hyperallometric

Meaning and significance not clear – please clarify

Why is the analysis of the role of vertebral arteries limited to the supplement? The scientific questions of greatest interest are not the role of ICA blood flow as a supply for brain metabolism, but for all blood flow. Granted, VA dimensions are not available for fossil specimens, but the crux of that analysis and the authors' interpretation and take away should be summarized in the

main paper. In addition, the authors stop short of discussing the significance of that analysis and their conclusions even in the supplement, which seems to be written solely for Boyer and Harrington as audience. Please explain what was found and the take away from that analysis, which were confusing to me as written.

Figure 2 – it looks like pongo, pan and gorilla are a nudge outside the 95% confidence interval for haplorrhine primates? Perhaps this is trivial - but it should be discussed.

Decision letter (RSPB-2019-1443.R0)

30-Jul-2019

Dear Dr Seymour:

I am writing to inform you that your manuscript RSPB-2019-1443 entitled "Brain perfusion by the internal carotid arteries is greater in modern great apes than in *Australopithecus*" has, in its current form, been rejected for publication in Proceedings B.

This action has been taken on the advice of referees, who have recommended that substantial revisions are necessary. With this in mind we would be happy to consider a resubmission, provided the comments of the referees are fully addressed. However please note that this is not a provisional acceptance. Indeed, substantive revisions are required to satisfy both reviewers and the Associate Editor.

The resubmission will be treated as a new manuscript. However, we will approach the same reviewers if they are available and it is deemed appropriate to do so by the Editor. Please note that resubmissions must be submitted within six months of the date of this email. In exceptional circumstances, extensions may be possible if agreed with the Editorial Office. Manuscripts submitted after this date will be automatically rejected.

Please find below the comments made by the referees, not including confidential reports to the Editor, which I hope you will find useful. If you do choose to resubmit your manuscript, please upload the following:

1) A 'response to referees' document including details of how you have responded to the comments, and the adjustments you have made.
2) A clean copy of the manuscript and one with 'tracked changes' indicating your 'response to referees' comments document.
3) Line numbers in your main document.

To upload a resubmitted manuscript, log into http://mc.manuscriptcentral.com/prsb and enter your Author Centre, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Resubmission." Please be sure to indicate in your cover letter that it is a resubmission, and supply the previous reference number.

In your revision process, please take a second look at how open your science is; our policy is that all data involved with the study should be made openly accessible-- see:
https://royalsociety.org/journals/ethics-policies/data-sharing-mining/

Insufficient sharing of data can delay or even cause rejection of a paper.

Sincerely,

Professor John Hutchinson, Editor
mailto: proceedingsb@royalsociety.org

Associate Editor
Board Member: 1
Comments to Author:
This paper uses arterial foramina morphology in the skulls of living primates as an osteological correlate for blood flow rate and brain metabolic rate. Having established this link between osteology and function the authors apply to interpret the evolution of neurological capabilities in fossil hominids. My first impression on reading this paper was that it represents a very nice approach to a very important and topical area of evolutionary biology. I'm not an expert in this specific field, but it appears that this general impression is shared by the reviewers, who are very positive about the paper and its specifics. However, both reviewers do highlight similar issues with the paper that prohibit publication in its current form. In particular, the authors should tackle the issue, raised by both reviewers, with their interpretation of the evolutionary scenario within early hominins versus other lineages. My recommendation is that the authors attempt to tackle the issues raised by the reviewers in a resubmission.

Reviewer(s)' Comments to Author:

Referee: 1

Comments to the Author(s)
Seymore et al. present a novel analysis of the relationship between perfusion rate through the internal carotid arteries and brain size, as measured by endocranial volume, in primates with a particular focus upon hominins as compared to the other great apes. The data represent some novel data from nine species of great ape, together with a re-analysis of significant published raw data on a range of haplorhines from multiple sources. The re-analysis method is novel and important as it for the first time uses a recently published empirical data-derived formula to calculate blood flow rate in the internal carotid arteries from raw foramen radius measurements. This empirical approach is applied here to haplorhines and hominins for the first time. Seymore et al. report that extinct hominins comparable in brain size to non-human great apes possess relatively much lower rates of perfusion through the internal carotid artery. They further report that the relative rate of increase in brain perfusion during hominin evolution is significantly different to that observed across the rest of haplorhine primates. This is a novel and interesting finding with potentially wide implications. There are however significant issues with the way that the data are presented and the way that they are interpreted (see below). If these can be addressed, then this work would certainly be of interest to the readership of Proceedings B.

Major revisions

Results

Figure 1 essentially represents a zoom in of the region of figure 2 that corresponds to the top right region of figure 2 that contains the extant great apes and the fossil hominins. Why is

Australopithecus the only extinct hominin shown in this figure? Surely the conclusions of the paper relate not only to Australopithecus but also to all of the other extinct hominins with approximately similar ECVs? In the present form, figure 1 appears as a selectively presented subset of figure 2. Given this, it would make much more sense to present the current figure 2 as the first figure, and an expanded current figure 1 (ie. with all extinct hominins in both the linear and logarithmic plots) as the second figure.

Discussion

Final paragraph: the interpretation that the authors propose is confused. They seem to be suggesting that the different great ape lineages evolved enhanced cognitive ability, and therefore greater QICA relative to brain size, independently of one another and of hominins ie. multiple independent evolution of social groups and enhanced cognitive ability (lines 194-196). It is more parsimonius, and more plausible, to posit that the LCA of the great apes had high relative QICA, and accompanying cognitive and social abilities, as did all subsequent lineages of great apes apart from the human lineage after it split with the chimp-human LCA 6-7.5 mya. Thus, the human lineage took an unusual trajectory after splitting from the chimp lineage.

This interpretation would correlate with evidence for increased expansion of the pre-frontal cortex (and its associations with social/group intelligence) in the ancestor of the great apes (Smaers et al. 2017 Current Biology). A relative decrease in QICA in the human lineage after it diverged from chimps and then a subsequent steeper increase in QICA relative to brain size, the central arguement of this paper (figure 2), would also correlate with the abundant recent evidence for significant genetic and developmental differences that evolved in the human lineage after it separated from the chimp lineage (eg. Dennis et al. 2012 Cell, Charrier et al. 2012 Cell, Florio et al. 2015 Science, Ju et al. 2016 Elife, Fiddes et al. 2018 Cell, Suzuki et al. 2018 Cell, Pollen et al. 2019 Cell) that are also associated with cognition and social behaviour in humans (Doan et al. 2016 Cell).

Minor revisions

Abstract

Line 6: The statement that the ICAs supply 'most of the primate cerebrum' is an oversimplification, since the cerebral arterial blood supply derives from the Circle of Willis, an anastomosis supplied by the ICAs and the basilar artery.

Introduction

33: should read 'glucose use across several mammalian species…'

42-44: The wording here of the comparison between cephalic and lower body circulation ration between arterial wall thickness and lumen radius is confused. The ratio would indeed be higher for lower body circulation, but would be still be constant, and the extension of LaPlace's law is therefore no less valid.

Results

77-79: The data point for Australopithecus does not simply sit below the linear regression

intervals for the extant taxa, but is far far below. The text should be altered to add emphasis to this finding.

84: The value of 0.3 for the ratio of the ICA to the carotid foramen is only explained in the legend to figure S4. It should be made clear in the main text how this ratio was derived.

108: a figure is given for the scaling exponent in mammals in general as 0.86, but it should be made clear where this data is derived from ie. with a citation.

Discussion

136-137: Assuming that extant taxa represent conditions of their ancestors is not a sensible assumption, especially in the evolutionary history of the haplorhine cortex. This should be re-phrased so as to be more precise ie. indicating that by inference from the data from extant haplorhines, we see an increase in brain size and complexity across evolutionary time on the human lineage.

141-142: the authors should avoid phrases such as 'are the oldest' in relation to lineages; all lineages are the same age. Rather they should refer to the particular characteristics in question in terms of age eg. the large brains seen in the hominoid lineage have a more recent evolutionary origin than the smaller brains found in extant platyrrhines.

144-145: The authors contend that the level of cortical foliation increased at a faster rate than brain volume. What is this based upon? It is not obvious that any measure of foliation (eg. foliation index) is directly comparable to volume and therefore this statement seems unwarranted.

152-154: Comparing the metabolic activity of grey matter and white matter is something of a false dichotomy, since much of the metabolic activity of projection neurons that supports the axon (white matter) occurs in the cell body (grey matter), but long axons contribute hugely to the metabolic needs of projection neurons. This sentence should be removed.

168-171: The date of the human-chimp LCA does not directly inform the cognitive evolution in the lineage of the LCA of the great apes, since the LCA of great apes lived ~15-20 MYA. This should be re-written.

173: the authors should refrain from referring to 'cognitive' parts of the brain that exclude the cerebellum, and instead refer to the neocortex or telencephalon (as shown in figure 3).

187-188: The final sentence in this paragraph rather undermines the central assumption that underlies the conclusions of the paper, namely that QICA can act as a proxy for cognitive ability. As such, this warrants a more thorough discussion.

Methods

Line204: 9 species of great ape (ie. including hominins) are listed in table S2 as being the source of the novel data, not 6 as is stated in the text.

Supplementary text

Computational approaches to evaluate blood flow rate from foramen size

Paragraph 2: the authors state that 'Central mean arterial blood pressure is practically

independent of body mass in mammals the size of primates.' This is a vague statement and should be justified properly.

ICA blood flow calculated with the shear stress and empirical equations

Paragraph 1: The authors contend that the use of w=0.3 in the empirical equation increases the QICA by 25% in hominins, citing figure S2. However, S2 compares QICA to ECV for hominins and does not include data on the mean and standard error of values for QICA as calculated using the different equations.

Paragraph 3: Again, the reference to the 'cognitive parts' of the brain here are not warranted for the same reason as above (Discussion, line 173).

Roles of the ICAs and VAs in total brain perfusion in hominins

Paragraph 1: The authors discuss published and unpublished data suggesting that the majority of cerebral perfusion and flow derives from the ICAs. This is certainly true, but it does not follow that 'the ICAs are relied upon for servicing almost all of the cognitive parts of the human brain. The VAs supply mainly the upper spinal cord, brainstem and cerebellum.' Given the anastomotic relationship between the ICAs, the VAs, and the cerebral circulation, this inference is not warranted. Secondly, given the evidence of recent years (eg Diedrichsen et al. 2019 Neuron), it is not true to imply that the cerebellum is not a 'cognitive' part of the brain. The inference of different cephalic spatial perfusions of ICAs vs VAs should be removed from the text.

Paragraph 2: The explanations behind the authors' inferences of QVA in fossil hominins is not clear. This explanation is aimed at the non-specialist, and so should not assume a working relationship with allometric power equations. In particular, the distinction between factors and terms should be elaborated and made clearer.

Figures

Figure 2

The red dots presumably represent the 12 species of hominins. The figure legend should make this explicit.

Figure S1

Confidence intervals are not reported for these plots. Despite the fact that there is not a significant difference in the exponents between the groups plotted, confidence intervals should nevertheless be shown.

Figure S3 & S4

It should be indicated in the legend which line of correlation line applies to which dataset.

Referee: 2

Comments to the Author(s)
This is an important and interesting question, harnessing methods that the authors have been instrumental in developing. While I love the premise and approach, I'm having trouble

envisioning the evolutionary trajectories that would be necessary to explain the authors' findings and to support their interpretation.

There is a fairly well-defined allometry linking Qica and endocranial volume (defining perfusion) in extant Haplorhine primates. Humans are on that line, as are (although perhaps slightly below, see note below) the other extant great apes. But the fossil hominins are not – they follow their own slope and only converge with the haplorhine line at the upper extreme of cranial capacity represented by modern humans.

If we assume (as the authors reasonably do) that the smaller brained/earlier hominins (australopiths) are likely representative of e.g. the human-pan LCA, this implies that chimps and humans had an ancestor with a cerebral perfusion below that predicted by the more general haplorhine allometry, and that the lineages leading to pan and human then increased blood perfusion in parallel in a fashion that somehow ended up (with humans and living pan species) converging with the extant haplorhine allometry.

How do 44 species of Haplorhine primates, including humans and other extant great apes, end up adhering to a consistent scaling relationship between Qica and cranial volume, while some of the ancestors of a few of those species (humans, and likely, pan) were on a different allometry, with a markedly different slope, until recently? Would it not require the evolution of a derived reduction in cerebral perfusion (implying reduced cognitive abilities for brain and body size than e.g. OWM) specific to early ancestral apes that was reversed in human and pan – and with the latter more recently converging with the haplorhine allometry as a mere coincidence? Is it not parsimonious to assume that there is something "off" about the hominin allometry reconstructed from fossil specimens? At a minimum, I think this possibility should be entertained. Perhaps I am missing some obvious interpretation, but the pattern of findings that the authors report strikes me as difficult to explain.

The authors grapple with this in the final paragraph:
The high cerebral perfusion may relate to modern great apes living in social family groups
190 that require complex understanding of family interrelationship and hierarchies [40]. Such family
191 structures demand a higher degree of cognitive capacity to partake in social behaviours that would
192 render individuals fit for mating and territory defence, in comparison to solitary mammals [41, 42].

>That is fine – but all extant Haplorhine, not just modern great apes, adhere to a common allometry. This is not acknowledged or discussed, but should be (this is what is most paradoxical and difficult to explain)

193 Such social drivers for cognitive evolution are often attributed to Australopithecus and early Homo.
194 However, the presumption that the same predecessor of great apes and humans did not exhibit as
195 complex family cooperation as modern great apes would suggest that great apes evolved this life
196 history trait in parallel with hominins. This would have contributed to increases in ancestral great
197 ape cerebral metabolic and ICA blood flow rates, in a similar way to the Homo predecessors. It can
198 be argued that the cognitive capacity that favoured the survival of the genus Homo equally

199 facilitated the survival of ancestral great apes. The requirement for cerebral specialisation may have
200 ultimately contributed to modern great apes being more cognitively advanced than
201 Australopithecus.

 Right – but again, these hypothesized derived levels of "high" blood flow that were proposed to evolve in parallel in the various great ape lineages are actually not high but just what would be predicted for haplorhines of their brain size…again, hard to explain this.

Specific points:

The implication of these
117 disparate results is that the position of the human brain appears to be an isometric ("a scaled up")
118 version of a haplorhine primate brain, something noticed previously [22-24], but the trajectory of its
119 evolution among hominins is quite hyperallometric

Meaning and significance not clear – please clarify

Why is the analysis of the role of vertebral arteries limited to the supplement? The scientific questions of greatest interest are not the role of ICA blood flow as a supply for brain metabolism, but for all blood flow. Granted, VA dimensions are not available for fossil specimens, but the crux of that analysis and the authors' interpretation and take away should be summarized in the main paper. In addition, the authors stop short of discussing the significance of that analysis and their conclusions even in the supplement, which seems to be written solely for Boyer and Harrington as audience. Please explain what was found and the take away from that analysis, which were confusing to me as written.

Figure 2 – it looks like pongo, pan and gorilla are a nudge outside the 95% confidence interval for haplorrhine primates? Perhaps this is trivial - but it should be discussed.

Author's Response to Decision Letter for (RSPB-2019-1443.R0)

See Appendix A.

RSPB-2019-1897.R0

Review form: Reviewer 1

Recommendation
Major revision is needed (please make suggestions in comments)

Scientific importance: Is the manuscript an original and important contribution to its field?
Good

General interest: Is the paper of sufficient general interest?
Excellent

Quality of the paper: Is the overall quality of the paper suitable?
Acceptable

Is the length of the paper justified?
Yes

Should the paper be seen by a specialist statistical reviewer?
No

Do you have any concerns about statistical analyses in this paper? If so, please specify them explicitly in your report.
No

It is a condition of publication that authors make their supporting data, code and materials available - either as supplementary material or hosted in an external repository. Please rate, if applicable, the supporting data on the following criteria.

Is it accessible?
Yes

Is it clear?
Yes

Is it adequate?
Yes

Do you have any ethical concerns with this paper?
No

Comments to the Author
The authors have taken on board the criticisms in relation to the comments made and addressed them partially, or made intelligent counter arguments. The manuscript is now much improved, and figure 4 certainly adds to the quality of the manuscript. The authors also make explicit their contention that the great ape lineages independently increased their relative QICA (and, by inference, brain metabolic rate) independently, with the great ape, human-gorilla, and human-chimp LCAs all having a low QICA relative to brain size (in line with that seen in Ardipithecus, figure 4), but with this increase having a much steeper gradient in the human lineage. I remain uncomfortable with the inference of social group size being related to this increase (lines 162-169) as it seems a stretch to contend that the human-chimp, human-gorilla and great ape LCAs all did not exhibit complex family cooperation (line 168).

While the authors have outlined more explicitly the implications of their data in relation to all haplorhines (paragraph beginning at line 184) and acknowledged that the lack of non-hominin haplorhine fossil ICA data is problematic, they have still not addressed the fact that this allometric ratio of QICA to brain volume in the hominin lineage is unusual when compared to that across the rest of the extant haplorhines (figure 2), and by implication, their various LCAs. Surely there must be some reason for the unusual gradient of allometry in hominins? Is it possible that this unusual relationship is a feature of the progression towards particularly large

brains (in absolute terms) for some reason? Might this also explain the anomalous position of smaller recent species in figure 4 (H.floresiensis and H.naledi)?

Finally, in response to referee 2's final question regarding the position below the confidence intervals of the extant non-human great apes (figure 2), the authors imply that the data used in figure 2 is from 'the older data for these species' and that the 'present data for for Pongo, Pan and Gorilla, involving much larger sample sizes... ...would be within the confidence belts'. If this is true, then why is this present data not plotted in figure 2?

Review form: Reviewer 2

Recommendation
Accept with minor revision (please list in comments)

Scientific importance: Is the manuscript an original and important contribution to its field?
Excellent

General interest: Is the paper of sufficient general interest?
Excellent

Quality of the paper: Is the overall quality of the paper suitable?
Good

Is the length of the paper justified?
Yes

Should the paper be seen by a specialist statistical reviewer?
Yes

Do you have any concerns about statistical analyses in this paper? If so, please specify them explicitly in your report.
No

It is a condition of publication that authors make their supporting data, code and materials available - either as supplementary material or hosted in an external repository. Please rate, if applicable, the supporting data on the following criteria.

Is it accessible?
Yes

Is it clear?
Yes

Is it adequate?
Yes

Do you have any ethical concerns with this paper?
No

Comments to the Author
The authors have mostly addressed my suggestions. That said, I remain perplexed by the core finding that the hominin lineage follows a distinct evolutionary trajectory of brain perfusion, with early hominin brains using far less energy per gram of brain tissue than contemporary haplorhines (including humans and great apes). I think it would be wise for the authors to discuss alternative interpretations to explain these findings. Perhaps the most obvious possibility is that the vertebral artery, which is not included in the main analyses presented here, provided a larger fraction of total cerebral blood flow among ancestral hominins. The authors include the following statement: "The 1.41 exponent for QICA is so high that it cannot be compensated by flow in the vertebral arteries to achieve even isometric total brain perfusion in hominins" Analysis of the possible contribution of VA blood flow is in the supplement and otherwise not discussed in the main paper. It would be useful to include a brief quantitative summary of how the authors reached their conclusion (this is not obvious looking at allometries plotted on log-log plots). In the supplement the authors note that the vertebral artery accounts for around 25% of total cerebral blood flow in humans. A paper not cited (Wu, C., Honarmand, A.R., Schnell, S., Kuhn, R., Schoeneman, S.E., Ansari, S.A., Carr, J., Markl, M. and Shaibani, A., 2016. Age-related changes of normal cerebral and cardiac blood flow in children and adults aged 7 months to 61 years. Journal of the American Heart Association, 5(1), p.e002657.) has BA blood flow at approximately equal to left or right ICA blood flow - so likely closer to one-third of TCBF. Moreover, there is no VA foramina info available for the hominin species included. It is thus possible that hominins have followed a distinct evolutionary trajectory in the relative contribution of VA vs. ICA as supplies of cerebral blood flow. In my view, this seems a potentially more parsimonious hypothesis than the one advanced by the authors, which requires multiple lineages to converge on a similar contemporary allometry by chance. In short, I feel that the authors should devote a bit more space to discussing alternative possible interpretations for their findings.

Decision letter (RSPB-2019-1897.R0)

11-Sep-2019

I am writing to inform you that this version of your manuscript RSPB-2019-1897 entitled "Cerebral blood flow rates in recent great apes are greater than occurred in australopithecine human relatives that had equal or larger brains" has, in its current form, been rejected for publication in Proceedings B.

This action has been taken on the advice of referees, who have recommended that substantial revisions are necessary. With this in mind we would be happy to consider a resubmission, provided the comments of the referees are fully addressed. However please note that this is not a provisional acceptance.

The resubmission will be treated as a new manuscript. However, we will approach the same reviewers if they are available and it is deemed appropriate to do so by the Editor. Please note that resubmissions must be submitted within six months of the date of this email. In exceptional circumstances, extensions may be possible if agreed with the Editorial Office. Manuscripts submitted after this date will be automatically rejected.

Please find below the comments made by the referees, not including confidential reports to the Editor, which I hope you will find useful.

Please find below the comments made by the referees, not including confidential reports to the Editor, which I hope you will find useful. If you do choose to resubmit your manuscript, please upload the following:

1) A 'response to referees' document including details of how you have responded to the comments, and the adjustments you have made.
2) A clean copy of the manuscript and one with 'tracked changes' indicating your 'response to referees' comments document.
3) Line numbers in your main document.

To upload a resubmitted manuscript, log into http://mc.manuscriptcentral.com/prsb and enter your Author Centre, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Resubmission." Please be sure to indicate in your cover letter that it is a resubmission, and supply the previous reference number.

In your revision process, please take a second look at how open your science is; our policy is that all data involved with the study should be made openly accessible-- see:
https://royalsociety.org/journals/ethics-policies/data-sharing-mining/
Insufficient sharing of data can delay or even cause rejection of a paper.

Sincerely,

Professor John Hutchinson, Editor
mailto: proceedingsb@royalsociety.org

Associate Editor
Comments to Author:
The authors have mostly addressed the comments made on their last submission. However, the reviewers are unanimous in their opinion that more serious attention needs to be paid to alternative mechanistic explanations for the trends identified herein. And I agree. In my view, diluting their currently favoured explanatory hypothesis would benefit the paper, rather than negatively impacting on its significance. I recommend the authors address the reviewers concerns directly in a resubmission.

Reviewer(s)' Comments to Author:

Referee: 1

Comments to the Author(s).
The authors have taken on board the criticisms in relation to the comments made and addressed them partially, or made intelligent counter arguments. The manuscript is now much improved, and figure 4 certainly adds to the quality of the manuscript. The authors also make explicit their contention that the great ape lineages independently increased their relative QICA (and, by inference, brain metabolic rate) independently, with the great ape, human-gorilla, and human-chimp LCAs all having a low QICA relative to brain size (in line with that seen in Ardipithecus, figure 4), but with this increase having a much steeper gradient in the human lineage. I remain uncomfortable with the inference of social group size being related to this increase (lines 162-169) as it seems a stretch to contend that the human-chimp, human-gorilla and great ape LCAs all did not exhibit complex family cooperation (line 168).

While the authors have outlined more explicitly the implications of their data in relation to all haplorhines (paragraph beginning at line 184) and acknowledged that the lack of non-hominin

haplorhine fossil ICA data is problematic, they have still not addressed the fact that this allometric ratio of QICA to brain volume in the hominin lineage is unusual when compared to that across the rest of the extant haplorhines (figure 2), and by implication, their various LCAs. Surely there must be some reason for the unusual gradient of allometry in hominins? Is it possible that this unusual relationship is a feature of the progression towards particularly large brains (in absolute terms) for some reason? Might this also explain the anomalous position of smaller recent species in figure 4 (H.floresiensis and H.naledi)?

Finally, in response to referee 2's final question regarding the position below the confidence intervals of the extant non-human great apes (figure 2), the authors imply that the data used in figure 2 is from 'the older data for these species' and that the 'present data for for Pongo, Pan and Gorilla, involving much larger sample sizes... ...would be within the confidence belts'. If this is true, then why is this present data not plotted in figure 2?

Referee: 2

Comments to the Author(s).
The authors have mostly addressed my suggestions. That said, I remain perplexed by the core finding that the hominin lineage follows a distinct evolutionary trajectory of brain perfusion, with early hominin brains using far less energy per gram of brain tissue than contemporary haplorhines (including humans and great apes). I think it would be wise for the authors to discuss alternative interpretations to explain these findings. Perhaps the most obvious possibility is that the vertebral artery, which is not included in the main analyses presented here, provided a larger fraction of total cerebral blood flow among ancestral hominins. The authors include the following statement: "The 1.41 exponent for QICA is so high that it cannot be compensated by flow in the vertebral arteries to achieve even isometric total brain perfusion in hominins" Analysis of the possible contribution of VA blood flow is in the supplement and otherwise not discussed in the main paper. It would be useful to include a brief quantitative summary of how the authors reached their conclusion (this is not obvious looking at allometries plotted on log-log plots). In the supplement the authors note that the vertebral artery accounts for around 25% of total cerebral blood flow in humans. A paper not cited (Wu, C., Honarmand, A.R., Schnell, S., Kuhn, R., Schoeneman, S.E., Ansari, S.A., Carr, J., Markl, M. and Shaibani, A., 2016. Age-related changes of normal cerebral and cardiac blood flow in children and adults aged 7 months to 61 years. Journal of the American Heart Association, 5(1), p.e002657.) has BA blood flow at approximately equal to left or right ICA blood flow - so likely closer to one-third of TCBF. Moreover, there is no VA foramina info available for the hominin species included. It is thus possible that hominins have followed a distinct evolutionary trajectory in the relative contribution of VA vs. ICA as supplies of cerebral blood flow. In my view, this seems a potentially more parsimonious hypothesis than the one advanced by the authors, which requires multiple lineages to converge on a similar contemporary allometry by chance. In short, I feel that the authors should devote a bit more space to discussing alternative possible interpretations for their findings.

Author's Response to Decision Letter for (RSPB-2019-1897.R0)

See Appendix B.

RSPB-2019-2208.R0

Review form: Reviewer 1

Recommendation
Accept as is

Scientific importance: Is the manuscript an original and important contribution to its field?
Good

General interest: Is the paper of sufficient general interest?
Excellent

Quality of the paper: Is the overall quality of the paper suitable?
Good

Is the length of the paper justified?
Yes

Should the paper be seen by a specialist statistical reviewer?
No

Do you have any concerns about statistical analyses in this paper? If so, please specify them explicitly in your report.
No

It is a condition of publication that authors make their supporting data, code and materials available - either as supplementary material or hosted in an external repository. Please rate, if applicable, the supporting data on the following criteria.

Is it accessible?
Yes

Is it clear?
Yes

Is it adequate?
Yes

Do you have any ethical concerns with this paper?
No

Comments to the Author
The authors have simplified their discussion in relation to great ape cognitive evolution, and this significantly improves the manuscript. They have also included a wide-ranging discussion of the potential (or lack thereof) contributions that VA perfusion may have made to the observations made in the paper in relation to the ICA. This again significantly improves the manuscript, and I now recommend publication.

Decision letter (RSPB-2019-2208.R0)

14-Oct-2019

Dear Dr Seymour

I am pleased to inform you that your manuscript RSPB-2019-2208 entitled "Cerebral blood flow rates in recent great apes are greater than in Australopithecus species that had equal or larger brains" has been accepted for publication in Proceedings B. Congratulations!

The referee(s) have recommended publication, but also suggest some minor revisions to your manuscript. Therefore, I invite you to respond to the referee(s)' comments and revise your manuscript. Because the schedule for publication is very tight, it is a condition of publication that you submit the revised version of your manuscript within 7 days. If you do not think you will be able to meet this date please let us know.

To revise your manuscript, log into https://mc.manuscriptcentral.com/prsb and enter your Author Centre, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision. You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript and upload a new version through your Author Centre.

When submitting your revised manuscript, you will be able to respond to the comments made by the referee(s) and upload a file "Response to Referees". You can use this to document any changes you make to the original manuscript. We require a copy of the manuscript with revisions made since the previous version marked as ‘tracked changes’ to be included in the ‘response to referees’ document.

Before uploading your revised files please make sure that you have:

1) A text file of the manuscript (doc, txt, rtf or tex), including the references, tables (including captions) and figure captions. Please remove any tracked changes from the text before submission. PDF files are not an accepted format for the "Main Document".

2) A separate electronic file of each figure (tiff, EPS or print-quality PDF preferred). The format should be produced directly from original creation package, or original software format. PowerPoint files are not accepted.

3) Electronic supplementary material: this should be contained in a separate file and where possible, all ESM should be combined into a single file. All supplementary materials accompanying an accepted article will be treated as in their final form. They will be published alongside the paper on the journal website and posted on the online figshare repository. Files on figshare will be made available approximately one week before the accompanying article so that the supplementary material can be attributed a unique DOI.

Online supplementary material will also carry the title and description provided during submission, so please ensure these are accurate and informative. Note that the Royal Society will not edit or typeset supplementary material and it will be hosted as provided. Please ensure that the supplementary material includes the paper details (authors, title, journal name, article DOI). Your article DOI will be 10.1098/rspb.[paper ID in form xxxx.xxxx e.g. 10.1098/rspb.2016.0049].

4) A media summary: a short non-technical summary (up to 100 words) of the key findings/importance of your manuscript.

5) Data accessibility section and data citation
It is a condition of publication that data supporting your paper are made available either in the electronic supplementary material or through an appropriate repository.

In order to ensure effective and robust dissemination and appropriate credit to authors the dataset(s) used should be fully cited. To ensure archived data are available to readers, authors should include a 'data accessibility' section immediately after the acknowledgements section. This should list the database and accession number for all data from the article that has been made publicly available, for instance:
• DNA sequences: Genbank accessions F234391-F234402
• Phylogenetic data: TreeBASE accession number S9123
• Final DNA sequence assembly uploaded as online supplemental material
• Climate data and MaxEnt input files: Dryad doi:10.5521/dryad.12311
NB. From April 1 2013, peer reviewed articles based on research funded wholly or partly by RCUK must include, if applicable, a statement on how the underlying research materials – such as data, samples or models – can be accessed. This statement should be included in the data accessibility section.

If you wish to submit your data to Dryad (http://datadryad.org/) and have not already done so you can submit your data via this link
http://datadryad.org/submit?journalID=RSPB&manu=(Document not available) which will take you to your unique entry in the Dryad repository. If you have already submitted your data to dryad you can make any necessary revisions to your dataset by following the above link.
Please see https://royalsociety.org/journals/ethics-policies/data-sharing-mining/ for more details.

6) For more information on our Licence to Publish, Open Access, Cover images and Media summaries, please visit https://royalsociety.org/journals/authors/author-guidelines/.

Once again, thank you for submitting your manuscript to Proceedings B and I look forward to receiving your revision. If you have any questions at all, please do not hesitate to get in touch.

Sincerely,
Professor John Hutchinson, Editor
mailto: proceedingsb@royalsociety.org

Reviewer(s)' Comments to Author:

Referee: 1

Comments to the Author(s).
The authors have simplified their discussion in relation to great ape cognitive evolution, and this significantly improves the manuscript. They have also included a wide-ranging discussion of the potential (or lack thereof) contributions that VA perfusion may have made to the observations made in the paper in relation to the ICA. This again significantly improves the manuscript, and I now recommend publication.

Decision letter (RSPB-2019-2208.R1)

21-Oct-2019

Dear Dr Seymour

I am pleased to inform you that your manuscript entitled "Cerebral blood flow rates in recent great apes are greater than in Australopithecus species that had equal or larger brains" has been accepted for publication in Proceedings B.

You can expect to receive a proof of your article from our Production office in due course, please check your spam filter if you do not receive it. PLEASE NOTE: you will be given the exact page length of your paper which may be different from the estimation from Editorial and you may be asked to reduce your paper if it goes over the 10 page limit.

If you are likely to be away from e-mail contact please let us know. Due to rapid publication and an extremely tight schedule, if comments are not received, we may publish the paper as it stands.

If you have any queries regarding the production of your final article or the publication date please contact procb_proofs@royalsociety.org

Your article has been estimated as being 9 pages long. Our Production Office will be able to confirm the exact length at proof stage.

Open Access
You are invited to opt for Open Access, making your freely available to all as soon as it is ready for publication under a CCBY licence. Our article processing charge for Open Access is £1700. Corresponding authors from member institutions (http://royalsocietypublishing.org/site/librarians/allmembers.xhtml) receive a 25% discount to these charges. For more information please visit http://royalsocietypublishing.org/open-access.

Paper charges
An e-mail request for payment of any related charges will be sent out shortly. The preferred payment method is by credit card; however, other payment options are available.

Electronic supplementary material:
All supplementary materials accompanying an accepted article will be treated as in their final form. They will be published alongside the paper on the journal website and posted on the online figshare repository. Files on figshare will be made available approximately one week before the accompanying article so that the supplementary material can be attributed a unique DOI.

Thank you for your fine contribution. On behalf of the Editors of the Proceedings B, we look forward to your continued contributions to the Journal.

Sincerely,
Proceedings B
mailto: proceedingsb@royalsociety.org

Appendix A

Referee comments and responses

Associate Editor
Board Member: 1
Comments to Author:
This paper uses arterial foramina morphology in the skulls of living primates as an osteological correlate for blood flow rate and brain metabolic rate. Having established this link between osteology and function the authors apply to interpret the evolution of neurological capabilities in fossil hominids. My first impression on reading this paper was that it represents a very nice approach to a very important and topical area of evolutionary biology. I'm not an expert in this specific field, but it appears that this general impression is shared by the reviewers, who are very positive about the paper and its specifics. However, both reviewers do highlight similar issues with the paper that prohibit publication in its current form. In particular, the authors should tackle the issue, raised by both reviewers, with their interpretation of the evolutionary scenario within early hominins versus other lineages. My recommendation is that the authors attempt to tackle the issues raised by the reviewers in a resubmission.
Response: Thank you for your positive response to the value of this paper and for recommending revision.

Reviewers' Comments to Author:

Referee: 1

Comments to the Author(s)
Seymore (sic) et al. present a novel analysis of the relationship between perfusion rate through the internal carotid arteries and brain size, as measured by endocranial volume, in primates with a particular focus upon hominins as compared to the other great apes. The data represent some novel data from nine species of great ape, together with a re-analysis of significant published raw data on a range of haplorhines from multiple sources. The re-analysis method is novel and important as it for the first time uses a recently published empirical data-derived formula to calculate blood flow rate in the internal carotid arteries from raw foramen radius measurements. This empirical approach is applied here to haplorhines and hominins for the first time. Seymore et al. report that extinct hominins comparable in brain size to non-human great apes possess relatively much lower rates of perfusion through the internal carotid artery. They further report that the relative rate of increase in brain perfusion during hominin evolution is significantly different to that observed across the rest of haplorhine primates. This is a novel and interesting finding with potentially wide implications. There are however significant issues with the way that the data are presented and the way that they are interpreted (see below). If these can be addressed, then this work would certainly be of interest to the readership of Proceedings B.
Response: We see that our initial submission caused some confusion between the rates of evolution and the allometric relationships between blood flow rate and endocranial volume. This is now clarified in the revised discussion and the addition of a new figure (details below).

Major revisions

Results

Figure 1 essentially represents a zoom in of the region of figure 2 that corresponds to the

top right region of figure 2 that contains the extant great apes and the fossil hominins. Why is Australopithecus the only extinct hominin shown in this figure? Surely the conclusions of the paper relate not only to Australopithecus but also to all of the other extinct hominins with approximately similar ECVs? In the present form, figure 1 appears as a selectively presented subset of figure 2. Given this, it would make much more sense to present the current figure 2 as the first figure, and an expanded current figure 1 (ie. with all extinct hominins in both the linear and logarithmic plots) as the second figure.

Response: The reasons that only the genus *Australopithecus* is analysed in Figure 1, are that *A. africanus* is the only species that we have sufficient replicates and the aim of the paper is to compare specifically non-human great apes and ancestors with similar brain size. A few *A. afarensis* were added to the genus. The other hominin species have only 1 – 3 replicates which are not adequate for statistics on any of them. We have retained the order of the figures, after careful thought, since figure 1 provides the most important findings of the study and should probably come first.

Discussion

Final paragraph: the interpretation that the authors propose is confused. They seem to be suggesting that the different great ape lineages evolved enhanced cognitive ability, and therefore greater QICA relative to brain size, independently of one another and of hominins ie. multiple independent evolution of social groups and enhanced cognitive ability (lines 194-196). It is more parsimonius, and more plausible, to posit that the LCA of the great apes had high relative QICA, and accompanying cognitive and social abilities, as did all subsequent lineages of great apes apart from the human lineage after it split with the chimp-human LCA 6-7.5 mya. Thus, the human lineage took an unusual trajectory after splitting from the chimp lineage.
We don't think that this proposal is plausible, because if the LCA of the great apes had a relatively high Qica, then it would have had to decrease to reach the low values apparent in *Ardipithecus* and *Australopithecus*. We think that the new figure we have provided (Fig. 4) makes it easy to visualize the evolution of this feature in hominins and chimpanzees.

This interpretation would correlate with evidence for increased expansion of the pre-frontal cortex (and its associations with social/group intelligence) in the ancestor of the great apes (Smaers et al. 2017 Current Biology). A relative decrease in QICA in the human lineage after it diverged from chimps and then a subsequent steeper increase in QICA relative to brain size, the central arguement of this paper (figure 2), would also correlate with the abundant recent evidence for significant genetic and developmental differences that evolved in the human lineage after it separated from the chimp lineage (eg. Dennis et al. 2012 Cell, Charrier et al. 2012 Cell, Florio et al. 2015 Science, Ju et al. 2016 Elife, Fiddes et al. 2018 Cell, Suzuki et al. 2018 Cell, Pollen et al. 2019 Cell) that are also associated with cognition and social behaviour in humans (Doan et al. 2016 Cell).
Thank you for the references, which we have studied, especially the one by Smaers et al. which is now mentioned in the revised discussion. The others concern genetic differences between humans and other living species. We are happy to let other anthropologists make these inferences about the evolution of the forebrain, but it is not necessary for the present paper that focuses on physiology.

Minor revisions

Abstract

Line 6: The statement that the ICAs supply 'most of the primate cerebrum' is an oversimplification, since the cerebral arterial blood supply derives from the Circle of Willis, an anastomosis supplied by the ICAs and the basilar artery.

Response: This issue is dealt with in the revised MS. We have a background meta-analysis for humans that quantifies the flow in the major cephalic arteries.

Introduction

33: should read 'glucose use across several mammalian species…'
Corrected.

42-44: The wording here of the comparison between cephalic and lower body circulation ration between arterial wall thickness and lumen radius is confused. The ratio would indeed be higher for lower body circulation, but would be still be constant, and the extension of LaPlace's law is therefore no less valid.
This sentence has been removed because it is not relevant at this stage of the MS.

Results

77-79: The data point for Australopithecus does not simply sit below the linear regression intervals for the extant taxa, but is far far below. The text should be altered to add emphasis to this finding.
The text has been changed and augmented to emphasize this result.

84: The value of 0.3 for the ratio of the ICA to the carotid foramen is only explained in the legend to figure S4. It should be made clear in the main text how this ratio was derived.
Thank you. We see that we did not mention this early enough. We have inserted this sentence into the introduction: "This ratio is taken as 0.30 for the internal carotid artery, based on 13 imaging studies on humans (See the Supplementary Material text and Table S1 for data and references.)"

108: a figure is given for the scaling exponent in mammals in general as 0.86, but it should be made clear where this data is derived from ie. with a citation.
Citation added.

Discussion
Largely due to both referee's responses, we have reorganised and rewritten large parts of the discussion, adding a new figure (Fig. 4) to enhance understanding.

136-137: Assuming that extant taxa represent conditions of their ancestors is not a sensible assumption, especially in the evolutionary history of the haplorhine cortex. This should be re-phrased so as to be more precise ie. indicating that by inference from the data from extant haplorhines, we see an increase in brain size and complexity across evolutionary time on the human lineage.
This is now clear in the revised discussion.

141-142: the authors should avoid phrases such as 'are the oldest' in relation to lineages; all lineages are the same age. Rather they should refer to the particular characteristics in question in terms of age eg. the large brains seen in the hominoid lineage have a more recent evolutionary origin than the smaller brains found in extant platyrrhines.
These two comments are taken on board with the new discussion.

144-145: The authors contend that the level of cortical foliation increased at a faster rate than brain volume. What is this based upon? It is not obvious that any measure of foliation (eg. foliation index) is directly comparable to volume and therefore this statement seems unwarranted.
We have added three references to gyrification and its association with intelligence:
Zilles K., Palomero-Gallagher N., Amunts K. 2013 Development of cortical folding during evolution and ontogeny. Trends in Neurosciences 36, 275-284.
Hofman M.A. 2014 Evolution of the human brain: when bigger is better. Frontiers in Neuroanatomy 8, e00015.
Gregory M., Kippenhan J., Dickinson D., Carrasco J., Mattay V., Weinberger D., Berman K. 2016 Regional variations in brain gyrification are associated with general cognitive ability in humans. Current Biology 26, 1301-1305.

152-154: Comparing the metabolic activity of grey matter and white matter is something of a false dichotomy, since much of the metabolic activity of projection neurons that supports the axon (white matter) occurs in the cell body (grey matter), but long axons contribute hugely to the metabolic needs of projection neurons. This sentence should be removed.
We provide two references on the differences in synaptic density and energy consumption of grey and white matter and two references that measured perfusion of regions of the brain considered to be grey and white matter. The sentence referred to here has been changed to note that the references indicate that grey matter is more highly perfused than white matter. The energy used for synaptic transmission is at least equal to that used for maintenance of membrane potential in axons and the functions of the non-neural cells of the brain. Because most synapses are in the grey matter, greater perfusion of grey matter seems reasonable.

168-171: The date of the human-chimp LCA does not directly inform the cognitive evolution in the lineage of the LCA of the great apes, since the LCA of great apes lived ~15-20 MYA. This should be re-written.
We have clarified this in the new discussion.

173: the authors should refrain from referring to 'cognitive' parts of the brain that exclude the cerebellum, and instead refer to the neocortex or telencephalon (as shown in figure 3).
Done.

187-188: The final sentence in this paragraph rather undermines the central assumption that underlies the conclusions of the paper, namely that QICA can act as a proxy for cognitive ability. As such, this warrants a more thorough discussion.
The discussion has been changed accordingly.

Methods

Line204: 9 species of great ape (ie. including hominins) are listed in table S2 as being the source of the novel data, not 6 as is stated in the text.
The sentence refers to the 6 species of non-hominid skulls measured in this study. The others were measured previously. The text now makes this clear.

Supplementary text

Computational approaches to evaluate blood flow rate from foramen size

Paragraph 2: the authors state that 'Central mean arterial blood pressure is practically independent of body mass in mammals the size of primates.' This is a vague statement and should be justified properly.
A statement involving the range of body mass from the cited reference is now added.

ICA blood flow calculated with the shear stress and empirical equations

Paragraph 1: The authors contend that the use of w=0.3 in the empirical equation increases the QICA by 25% in hominins, citing figure S2. However, S2 compares QICA to ECV for hominins and does not include data on the mean and standard error of values for QICA as calculated using the different equations.
The 25% figure comes from the ratio of scaling factors (0.000170 and 0.000373) evident in the equations in the legend to Figure S2. Because the exponents differ slightly, the word "approximately 25%" has been added to the text.

Paragraph 3: Again, the reference to the 'cognitive parts' of the brain here are not warranted for the same reason as above (Discussion, line 173).
"Cognitive parts" has been deleted.

Roles of the ICAs and VAs in total brain perfusion in hominins

Paragraph 1: The authors discuss published and unpublished data suggesting that the majority of cerebral perfusion and flow derives from the ICAs. This is certainly true, but it does not follow that 'the ICAs are relied upon for servicing almost all of the cognitive parts of the human brain. The VAs supply mainly the upper spinal cord, brainstem and cerebellum.' Given the anastomotic relationship between the ICAs, the VAs, and the cerebral circulation, this inference is not warranted. Secondly, given the evidence of recent years (eg Diedrichsen et al. 2019 Neuron), it is not true to imply that the cerebellum is not a 'cognitive' part of the brain. The inference of different cephalic spatial perfusions of ICAs vs VAs should be removed from the text.
Thank you for pointing this out to us and for the reference by Diedrichsen et al. Data for humans extracted from the larger meta-study of the relationship between blood flow rate and arterial size (Seymour et al. 2019) has been summarised in another paper that quantifies the proportions of total brain perfusion derived from the ICA and VA. Although these vessels do communicate in the circle of Willis, there is little flow in the communicating arteries, and the ICAs provide 75% of total brain perfusion and the VAs 25%. However, the ICAs provide 88% of the blood flow to the cerebrum. The paper is under consideration in another journal, but reference to that paper is not necessary, because the data are available in Seymour et al. 2019. The text has been modified to state this explicitly. We have also mentioned the proposal that the cerebellum has elements of cognitive function and cited the new reference. However, the Diedrichsen et al. paper does admit that communication with the cerebellum may be a developmental advantage, but not especially apparent in the adult brain.

Paragraph 2: The explanations behind the authors' inferences of QVA in fossil hominins is not clear. This explanation is aimed at the non-specialist, and so should not assume a

working relationship with allometric power equations. In particular, the distinction between factors and terms should be elaborated and made clearer.
Yes, we understand that many scientists are not comfortable with the manipulations of allometric equations. This is one reason why these matters are dealt with in the supplementary material. They are not essential to the paper yet should be presented to answer the question about the possible role of the VAs in hominin brain perfusion.

Figures

Figure 2

The red dots presumably represent the 12 species of hominins. The figure legend should make this explicit.
Done, both in the figure itself and the legend.

Figure S1

Confidence intervals are not reported for these plots. Despite the fact that there is not a significant difference in the exponents between the groups plotted, confidence intervals should nevertheless be shown.
We prefer to leave the figure unchanged. The statistics for the two relationships are given in the text and confidence belts are not necessary to show anything else and would clutter the figure unnecessarily. The same is true for Fig. S2, S3 and S4, where the relationships are particularly close to one another.

Figure S3 & S4

It should be indicated in the legend which line of correlation line applies to which dataset.
Done.

Referee: 2

Comments to the Author(s)
This is an important and interesting question, harnessing methods that the authors have been instrumental in developing. While I love the premise and approach, I'm having trouble envisioning the evolutionary trajectories that would be necessary to explain the authors' findings and to support their interpretation.

There is a fairly well-defined allometry linking Qica and endocranial volume (defining perfusion) in extant Haplorhine primates. Humans are on that line, as are (although perhaps slightly below, see note below) the other extant great apes. But the fossil hominins are not – they follow their own slope and only converge with the haplorhine line at the upper extreme of cranial capacity represented by modern humans.

If we assume (as the authors reasonably do) that the smaller brained/earlier hominins (australopiths) are likely representative of e.g. the human-pan LCA, this implies that chimps and humans had an ancestor with a cerebral perfusion below that predicted by the more general haplorhine allometry, and that the lineages leading to pan and human then

increased blood perfusion in parallel in a fashion that somehow ended up (with humans and living pan species) converging with the extant haplorhine allometry.

How do 44 species of Haplorhine primates, including humans and other extant great apes, end up adhering to a consistent scaling relationship between Qica and cranial volume, while some of the ancestors of a few of those species (humans, and likely, pan) were on a different allometry, with a markedly different slope, until recently? Would it not require the evolution of a derived reduction in cerebral perfusion (implying reduced cognitive abilities for brain and body size than e.g. OWM) specific to early ancestral apes that was reversed in human and pan – and with the latter more recently converging with the haplorhine allometry as a mere coincidence? Is it not parsimonious to assume that there is something "off" about the hominin allometry reconstructed from fossil specimens? At a minimum, I think this possibility should be entertained. Perhaps I am missing some obvious interpretation, but the pattern of findings that the authors report strikes me as difficult to explain.
Thank you for the quite reasonable comments. The previous text was not very clear about the distinction between the arrangement of species on an allometric line relating Qica and Vb (Fig. 2) and the evolution of those species. It is true that brain volume increased generally during evolution of the haplorhines, so the arrangement of the species on the allometric graph does reflect the order of evolution of the groups. However, these data are from recent species, not ancient ones. The fossil hominins also increased in brain size during evolution, so they too are arranged on the allometric figure in roughly the evolutionary order.
The solution is to create another figure (Fig. 4) that relates Qica to age of the hominin fossils. Over this are data for the great apes for comparison. This figure allows one to imagine the trajectories of the *Pan* lineage (as a representative great ape) and the gross hominin lineage.

The authors grapple with this in the final paragraph:
"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]."

>That is fine – but all extant Haplorhine, not just modern great apes, adhere to a common allometry. This is not acknowledged or discussed, but should be (this is what is most paradoxical and difficult to explain)
We think that the new Fig. 4 takes care of this point. We have rewritten and reorganised the discussion to help further.

"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."

¬ Right – but again, these hypothesized derived levels of "high" blood flow that were

proposed to evolve in parallel in the various great ape lineages are actually not high but just what would be predicted for haplorhines of their brain size…again, hard to explain this.

Again, the revised discussion and new Fig. 4. will help.

Specific points:

"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."

Meaning and significance not clear – please clarify
The sentence now states what the graphs look like first and uses the allometric terms and their definitions in brackets.

Why is the analysis of the role of vertebral arteries limited to the supplement? The scientific questions of greatest interest are not the role of ICA blood flow as a supply for brain metabolism, but for all blood flow. Granted, VA dimensions are not available for fossil specimens, but the crux of that analysis and the authors' interpretation and take away should be summarized in the main paper. In addition, the authors stop short of discussing the significance of that analysis and their conclusions even in the supplement, which seems to be written solely for Boyer and Harrington as audience. Please explain what was found and the take away from that analysis, which were confusing to me as written.
The supplementary text, analyses and figures are indeed in response to Boyer and Harrington, because their analysis is quite relevant to the subject here. Unfortunately, their analysis is a little misleading, so it is necessary to provide the correct allometric analysis in response to their paper. This allometric analysis is not central to our paper and it is quite technical , so would not be appreciated by most readers. In addition, this section includes a model of the role of the VAs, which might be somewhat difficult for those with little experience with allometric modelling to understand. So, in the discussion, we state: "The 1.41 exponent for 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.)

Figure 2 – it looks like pongo, pan and gorilla are a nudge outside the 95% confidence interval for haplorrhine primates? Perhaps this is trivial - but it should be discussed.
It is difficult for us to say anything about these three points from the old literature, because some of the other species of haplorhines are also below the confidence belts, sometimes even farther below the line. Also, the sample sizes for those points were relatively small. In fact, the present data for Pongo, Pan and Gorilla, involving much larger sample sizes, are higher than the older data for these species and would be within the confidence belts. We have considered this but make no change.

Appendix B

Referee's comments v2

Associate Editor
Comments to Author:
The authors have mostly addressed the comments made on their last submission. However, the reviewers are unanimous in their opinion that more serious attention needs to be paid to alternative mechanistic explanations for the trends identified herein. And I agree. In my view, diluting their currently favoured explanatory hypothesis would benefit the paper, rather than negatively impacting on its significance. I recommend the authors address the reviewers concerns directly in a resubmission.

We have addressed the comments of the referees, in particular with the addition of five paragraphs in the discussion concerning the roles of the vertebral arteries in total blood perfusion.

Reviewer(s)' Comments to Author:

Referee: 1

Comments to the Author(s).
The authors have taken on board the criticisms in relation to the comments made and addressed them partially, or made intelligent counter arguments. The manuscript is now much improved, and figure 4 certainly adds to the quality of the manuscript. The authors also make explicit their contention that the great ape lineages independently increased their relative QICA (and, by inference, brain metabolic rate) independently, with the great ape, human-gorilla, and human-chimp LCAs all having a low QICA relative to brain size (in line with that seen in Ardipithecus, figure 4), but with this increase having a much steeper gradient in the human lineage. I remain uncomfortable with the inference of social group size being related to this increase (lines 162-169) as it seems a stretch to contend that the human-chimp, human-gorilla and great ape LCAs all did not exhibit complex family cooperation (line 168).

Thank you for the comment, which refers to the paragraph on social units in great apes. We have removed the suggestion that the ancestors of great apes did not have social or family interactions, as this is not known for sure. However, it seems quite reasonable that social interactions may have led to greater cognitive ability in different hominid groups. There may be others, but this is the only evolutionary explanation we presently have for the results. We intentionally refrained from further speculation about the evolutionary behavioural correlates to the patterns of brain perfusion that we see. The focus in this paper is on the physiology.

While the authors have outlined more explicitly the implications of their data in relation to all haplorhines (paragraph beginning at line 184) and acknowledged that the lack of non-hominin haplorhine fossil ICA data is problematic, they have still not addressed the fact that this allometric ratio of QICA to brain volume in the hominin lineage is unusual when compared to that across the rest of the extant haplorhines (figure 2), and by implication, their various LCAs. Surely there must be some reason for the unusual gradient of allometry in hominins? Is it possible that this unusual relationship is a feature of the progression towards particularly large brains (in absolute terms) for some reason? Might this also explain the anomalous position of smaller recent species in figure 4 (H.floresiensis and H.naledi)?

We do not know how to answer the three questions posed here by this referee. We do not know why there is an apparent steep increase in brain perfusion in relation to brain size in the hominin lineage. It represents an increasing intensity of brain perfusion per gram of tissue, in contrast to the

more or less constant intensity we see between extant haplorhines. We have elaborated on this in the discussion by showing that the situation in hominins is not possibly similar to that of the haplorhines, even when considering the role of the vertebral artery. The model in the supplementary material, now discussed in the main paper, shows that it is unlikely that the vertebral arteries came to the rescue of a deficient ICA perfusion in *Australopithecus*. There is no physiological explanation for the difference between haplorhines and hominins. There is likely to be a behavioural explanation during hominin evolution, but we do not know what it is.

Finally, in response to referee 2's final question regarding the position below the confidence intervals of the extant non-human great apes (figure 2), the authors imply that the data used in figure 2 is from 'the older data for these species' and that the 'present data for for Pongo, Pan and Gorilla, involving much larger sample sizes... ...would be within the confidence belts'. If this is true, then why is this present data not plotted in figure 2?

The new data for haplorhines are plotted in Fig. 1. It is not necessary to plot it again in Fig. 2, which is from a different data set derived from the literature. If we included the new points for the great apes there, it would require recalculating the statistics, redrawing the figure while trying to differentiate old and new data in a tiny space on a large graph, and complicating the table of the data used. This would change the figure only slightly and would not change the conclusions at all. We do not see the benefit.

Referee: 2

Comments to the Author(s).
The authors have mostly addressed my suggestions. That said, I remain perplexed by the core finding that the hominin lineage follows a distinct evolutionary trajectory of brain perfusion, with early hominin brains using far less energy per gram of brain tissue than contemporary haplorhines (including humans and great apes). I think it would be wise for the authors to discuss alternative interpretations to explain these findings. Perhaps the most obvious possibility is that the vertebral artery, which is not included in the main analyses presented here, provided a larger fraction of total cerebral blood flow among ancestral hominins. The authors include the following statement: "The 1.41 exponent for QICA is so high that it cannot be compensated by flow in the vertebral arteries to achieve even isometric total brain perfusion in hominins" Analysis of the possible contribution of VA blood flow is in the supplement and otherwise not discussed in the main paper. It would be useful to include a brief quantitative summary of how the authors reached their conclusion (this is not obvious looking at allometries plotted on log-log plots). In the supplement the authors note that the vertebral artery accounts for around 25% of total cerebral blood flow in humans. A paper not cited (Wu, C., Honarmand, A.R., Schnell, S., Kuhn, R., Schoeneman, S.E., Ansari, S.A., Carr, J., Markl, M. and Shaibani, A., 2016. Age-related changes of normal cerebral and cardiac blood flow in children and adults aged 7 months to 61 years. Journal of the American Heart Association, 5(1), p.e002657.) has BA blood flow at approximately equal to left or right ICA blood flow - so likely closer to one-third of TCBF. Moreover, there is no VA foramina info available for the hominin species included. It is thus possible that hominins have followed a distinct evolutionary trajectory in the relative contribution of VA vs. ICA as supplies of cerebral blood flow. In my view, this seems a potentially more parsimonious hypothesis than the one advanced by the authors, which requires multiple lineages to converge on a similar contemporary allometry by chance. In short, I feel that the authors should devote a bit more space to discussing alternative possible interpretations for their findings.

We are glad that the referee recognises that the volume-specific perfusion (infer metabolic rate) is greater in extant haplorhines than in hominins. Because the idea comes from analysis of the ICA only, it is possible that the vertebral arteries (VA) were involved, as mentioned by referee 1. We

have addressed this problem with new paragraphs in the discussion. We first show that the VAs cannot compensate for low ICA flow using principles apparent in extant haplorhines. Then we focus on what a hypothetical VA would have to contribute in order to reach a normal total brain perfusion. Each refers to the earlier Supplementary Material, but the essence of the arguments are brought up in the revised discussion. We hope that this makes it clear.

The referee questions the 75-25% division between ICA and VA in the human brain. This is based on six references, but the referee supplies another one, apparently at variance with this division. However, the Wu et al. 2016 paper does not have data on BA flow rate versus ICA flow in it. There is only peak velocity for the vessels plotted with age. There are no measurements of arterial size or mean velocity. We have a paper specifically on human cephalic circulation back for a second review in the Journal of Anatomy, so we hope to refer to it directly in the present paper. However, the six references should be adequate.