

fit nicely with the known roles of RSPOs, LGRs and ubiquitin ligases. And, like people carrying *RSPO2* mutations, mice lacking *Rspo2* have limb abnormalities<sup>9</sup>. The authors expected that the loss of LGR activity would have the same effect. But they got a surprise when they analysed mice lacking the *Lgr4*, *5* and *6* genes — the triple-mutant embryos did not have limb or lung abnormalities. This suggests that, in some tissues, RSPO2 (and perhaps other RSPOs) can act independently of LGRs, potentiating WNT signalling in the absence of its usual binding partner.

To test this idea directly, the group next investigated whether cells isolated from LGR triple-mutant embryos are capable of RSPO-mediated WNT signalling. They found no evidence of WNT signalling when these cells were exposed to *Rspo1* or *Rspo4*, but WNT activity was detected in the presence of *Rspo2* or *Rspo3*. Thus, RSPO2 and RSPO3 seem to be able to induce WNT signalling independently of LGRs. However, these RSPOs still seem to act through their normal ubiquitin ligase targets, because Szenker-Ravi *et al.* found that modulation of ZNRF3 alters WNT signalling in triple-mutant cells. Consistent with this picture, the authors showed that deletion of *rspo2* in the frog *Xenopus laevis* led to missing limbs, whereas deletion of the *znrf3* and *rnf43* genes led to extra limbs.

This study demonstrates that the accepted model of WNT-receptor modulation does not hold in the case of limb and lung development. Szenker-Ravi *et al.* hypothesize that a separate, unidentified receptor is necessary for this LGR-independent WNT signalling (Fig. 1c). Notably, a study published earlier this year<sup>10</sup> identified one potential candidate. That work showed that RSPO2 and RSPO3 can bind to ZNRF3 or RNF43 in conjunction with heparin sulfate proteoglycan (HSPG) molecules in lieu of LGRs, to enable WNT signalling *in vitro*. Future work will be required to test whether HSPGs play this part in the context of lung and limb development. In addition, it remains to be determined whether the HSPG–RSPO–ZNRF3 complex promotes WNT signalling by preventing ZNRF3 activity, or whether another mechanism is at work. Either way, it will be important to determine the extent of any functional similarities between LGR- and HSPG-based complexes, and to uncover whether there is any pattern to the use of LGR or HSPG as a cofactor in a particular tissue.

Szenker-Ravi and colleagues' work also points to ways to broaden our understanding of processes that require WNT signalling, such as limb development. For example, analysis of the early stages of limb development in frog embryos lacking *znrf3* and *rnf43* could reveal why these mutations lead to extra limbs. Do ZNRF3 and RNF43 act as 'master regulators' of limb numbers, as the authors propose? Consistent with this idea, WNT activity has a role in initiating the formation of the limb bud<sup>11</sup> (which eventually gives rise to the limb).

Alternatively, rather than being master regulators, these proteins might mediate limb numbers indirectly. For example, extra limbs might arise as a secondary consequence of expansion of the pool of limb progenitor cells, or they might arise because of changes in the formation of a signalling centre at the tip of the limb bud that directs limb outgrowth — both WNT-dependent processes<sup>12,13</sup>.

Finally, it will be interesting to evaluate LGR-independent, RSPO-mediated WNT signalling in cancer. Chromosomal abnormalities that lead to activation of RSPO2 or RSPO3 have been shown to drive WNT-dependent colon tumours<sup>14</sup>. Szenker-Ravi and colleagues' demonstration that these two RSPOs can modulate WNT activity independent of LGR adds a twist to these findings, and should prompt scientists to look for cancer-causing mutations in RSPO2 or RSPO3 in cells outside LGR-expressing cell compartments. ■

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#### ANTHROPOLOGY

## Sizing up human brain evolution

An innovative computational analysis of factors that might have influenced human brain evolution suggests that ecological, rather than social, factors had a key role in the evolution of large, rapidly developing brains. [SEE LETTER P.554.](#)

RICHARD MCELREATH

Most organisms are brainless but thriving. Brains are expensive to produce and maintain, and in the human lineage they have grown so large as to incur a substantial metabolic burden as the brain develops<sup>1</sup>. A human brain stops growing by the age of ten, long before the body reaches physical maturity, and this costly and fast process of brain growth has been proposed to cause a delay in body growth<sup>1</sup>. Brain growth is not given priority in this way in other apes, and the human pattern is puzzling because it keeps our bodies smaller, more vulnerable and less productive for longer. The answer to this riddle must lie in how the human brain helped our ancestors to survive and reproduce. On page 554, González-Forero and Gardner<sup>2</sup> investigate the role of different factors as possible drivers of our unusually large brains, and determine how well these factors might account for the pattern of changes in brain and body size that occur as humans develop.

Proposals for how large brains evolved in humans include ecological, social and cultural hypotheses. The ecological-intelligence hypothesis suggests that environmental challenges,

such as finding food, are paramount in driving brain-size evolution<sup>3</sup>. The social-intelligence hypothesis suggests instead that the competitive and cooperative challenges of living with other members of the same species are the key factor<sup>4</sup>. The cultural-intelligence hypothesis combines these two ideas, suggesting that the social learning of ecologically relevant skills explains the extreme brain investment of our lineage<sup>5</sup>.

Until now, testing these hypotheses has relied mainly on comparative studies that correlate data on brain characteristics such as size (as an approximation of intelligence) with features such as cognition, ecology and group living. These regression approaches, which seek to identify variables that are associated with brain size, have been valuable for refining theories and the data measurements needed.

However, such regression studies can generate conflicting and confusing results. Changes to brain and body growth can have a reciprocal effect on each other for various reasons, such as metabolic constraints and energy-production needs, so such interactions between the brain and the body are complex and nonlinear. This makes the results of regression studies hard to interpret, because they cannot be connected directly to a relevant

evolutionary model. Researchers in the field should stop theorizing using one set of models while analysing data with another. Moving from purely statistical models, such as regression approaches, to studies that test evolutionary models could accelerate future progress.

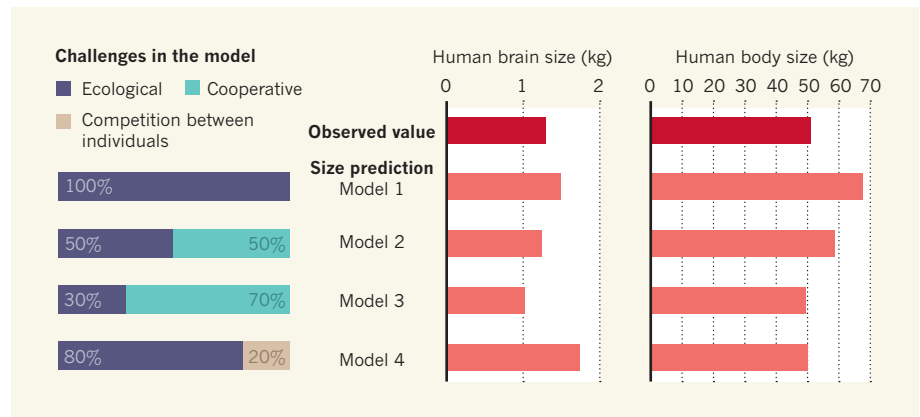
The study of human brain evolution must by necessity be observational, because direct experimentation to test the role of variables is not an option. But working out what affects different components in such observational systems is hard. When Ronald Fisher, a leading evolutionary biologist and statistician of the twentieth century, was asked how one could infer causality in such cases, his advice was to “make your theories elaborate”<sup>6</sup>.

Automobile engineering can provide an analogy for studying this type of system. It would be difficult to understand racing-car design through regression analysis of how engine size varies depending on changes in other features, such as the mass and shape of the car. Instead, a model is needed that uses physical laws to predict optimal combinations of the variables under different criteria. Understanding brain evolution poses a similar challenge in that an organism’s features co-evolve under biological constraints.

González-Forero and Gardner’s approach heeds Fisher’s advice because the authors generated an elaborate model to investigate brain evolution. Modelling brain evolution in this way can produce many precise predictions of brain size that can easily be falsified. And because the model is based on biological characteristics, it is easy to learn from it. When the model’s results do not match the observed evidence of brain size, the biological assumptions can be studied to understand why the model failed.

In the authors’ computational set-up, as a human individual ages, there is a schedule of investment in brain, body and reproductive tissue. As individuals grow, an increase in brain size allows for an increase in skill, and an increase in body size makes it easier to convert that skill into energy. The skill boost also aids successful reproduction. The model generates life-history scenarios that are linked to specific predictions of brain and body sizes.

The metabolic costs of maintaining bodies and brains were assigned in the model by using previously determined metabolic-scaling relationships, which provide information such as how the metabolic rate changes depending on an organism’s size. These metabolic costs were fixed in the authors’ model, and the importance of different types of challenge were estimated by varying the weighting of these challenges and assessing the subsequent effect on the predicted brain and body sizes (Fig. 1). The authors explored four types of challenge: ecological (me versus nature), cooperative ecological (us versus nature), between-individual competitive (me versus you), and between-group competitive (us versus them). The authors determined which combination of challenge weighting gave rise to a pattern of hypothetical brain and body growth



**Figure 1 | Modelling the evolution of human brain size.** Compared with other apes, humans have distinctively large and rapidly developing brains<sup>1</sup>, and how this human developmental pattern evolved is debated. González-Forero and Gardner<sup>2</sup> report a computational modelling analysis that investigates the role of ecological factors and social factors (such as cooperation or competition between individuals) in driving the evolution of human brain size. The authors’ model predicts human brain and body size depending on the relative weighting of ecological and social factors. Some examples of challenge weighting are shown to the left of the corresponding predictions generated in modelling results (data from Fig. 3 of ref. 2). Comparing such predicted values with the observed average brain and body size of a female adult enabled the authors to determine the relative importance of the evolutionary drivers, leading them to identify ecological drivers as being the major determinant of human brain size in their analysis.

that was most consistent with that observed during human life history.

González-Forero and Gardner’s analysis reveals a major role for ecological intelligence in driving human brain and body growth in this system. The best match between model predictions and observed human growth patterns came from assigning a weight of 60% to ecological challenges in the model.

By contrast, social challenges were less likely to contribute to the observed human growth patterns. Competitive challenges between individuals or groups are linked to large brains and to a body size that is smaller than the observed value. In competition, as skill increases, such gains in skill can lead to diminishing returns in terms of an increase in energy extraction because what each individual is competing against becomes continually harder to overcome. For example, skill increases in one individual could be matched by skill increases in other competitors, thereby limiting the energy boost from a skill increase. By contrast, the challenge itself doesn’t evolve in ecological challenges, so overcoming ecological challenges can lead to a more-efficient energy boost. The best-matched model had a 10% weight for between-group competition.

Cooperation was found to have more of an effect. The best-matched model assigns 30% weight to cooperative challenges. However, cooperation could lead to a reduction in brain size because individuals could potentially free-load on the intelligence of others, evidence of this effect has been observed in some animals<sup>7</sup>.

Ecological drivers are the clear winner. But the model fails to address the possible role of cultural intelligence, as the authors admit, because cultural dynamics are not included. The authors’ results are consistent with the cultural-intelligence hypothesis, but any such

possible connection remains speculative.

Some of the model’s size-prediction results are sensitive to the details, such as the precise way in which skill translates into reproductive success. However, this provides a valuable opportunity to understand previously unnoticed implications of hypotheses about the challenges driving brain evolution, and to identify targets for future work. For example, the model would benefit from more measurements of the rate at which skills increase with age, because few data of this kind currently exist.

Finally, because the model aims to explain brain size in humans only, the results have no clear significance for debates about the evolution of intelligence in other species. Nevertheless, the methodological implications of this work are enormous. This type of general framework to investigate and predict values for constellations of co-evolving variables, not only in adults but also throughout life, would allow for more-detailed tests of more-nuanced predictions, regardless of the species of interest. ■

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