Title:

Brain evolution and development: adaptation, allometry and constraint

Authors:

Stephen H. Montgomery[1], Nicholas I. Mundy[2], Robert A. Barton[3]

Affiliations:

[1] Dept. Genetics, Evolution & Environment, University College London, Gower Street, London, UK, WC1E 6BT

[2] Dept. of Zoology, University of Cambridge, St. Andrews Street, Cambridge, UK, CB2 3EJ

[3] Evolutionary Anthropology Research Group, Durham University, Dawson Building, South Road, Durham, UK, DH1 3LE

***Corresponding author**

Email: Stephen.Montgomery@cantab.net

Key words: adaptation, allometry, brain evolution, constraint, development

Abstract

Complex phenotypic traits are products of two processes: evolution and development. But how do these processes combine to produce integrated phenotypes? Comparative studies identify consistent patterns of co-variation, or allometries, between brain and body size, and between brain components, indicating the presence of significant constraints limiting independent evolution of the separate parts. These constraints are poorly understood, but in principle could be either developmental or functional. The developmental constraints hypothesis suggests that individual components (brain and body size, or individual brain components) tend to evolve together because natural selection operates on relatively simple developmental mechanisms that affect the growth of all parts in a concerted fashion. The functional constraints hypothesis suggests that correlated change reflects the action of selection on distributed functional systems connecting the different sub-components, predicting more complex patterns of mosaic change at the level of the functional systems and more complex genetic and developmental mechanisms. These hypotheses are not mutually exclusive but make different predictions. We review recent genetic and neuro-developmental evidence, concluding that functional rather than developmental constraints are the main cause of the observed patterns.

How brains evolve: the importance of scaling relationships

The components of any adaptive complex by definition undergo coordinated evolution. Brains, bodies and individual brain components, therefore exhibit distinctive patterns of correlated evolution. But what do these patterns tell us about the roles of adaptation and constraint in shaping phenotypes? In particular, how and to what extent do constraints imposed by shared developmental programs dictate allometric relationships between components, limiting their response to selection? These questions have shaped two key debates central to how we view brain evolution: the functional relevance of brain size, and the adaptive potential of brain structure (1–3). These debates hinge on whether observed patterns of scaling relationships, between brain and body size or different brain components, are the product of selection to maintain functional correspondence or constraints imposed by shared developmental programs. Crucially, however, a sound understanding of the significance of scaling relationships in brain evolution has been limited by a lack of data on the genetic and developmental mechanisms that regulate brain size and structure. Here we discuss how recent discoveries about the genetic control of neural development shed new light on the issue.

i) Brain:body co-evolution and the importance of size

One early conclusion of comparative neuroanatomy was the simple observation that animals with larger bodies have larger brains (4). Deviation from this pattern may reveal levels of 'cephalisation', or 'progressive' brain expansion, reflecting cognitive ability (4). This has led to models of brain evolution that emphasize 'passive growth', caused by an indirect response to selection on body size, and 'active growth' that increases brain size relative to body size (5). However, there is minimal evidence as to how the joint developmental control of brain and body size could be achieved. Brain and body development have notably different ontogenetic trajectories; for example in mammals brain growth ceases long before body growth, and prenatal brain growth, during which the majority of neurogenesis occurs, is evolutionarily and genetically dissociable from postnatal brain growth (6–9) In other vertebrate groups where the brain continues to grow continuously through adulthood, brain and body growth trajectories may still vary. For example, brain growth is continuous in Crocodilians but slows with age, relative to body growth (10) Any developmental mechanism that coordinates brain and body size must therefore act at multiple developmental stages,

and in multiple tissues. Whilst several hypotheses have been suggested, from developmental programming which fixes the number of cycles a neural progenitor cell can undergo (11), to growth-hormone mediated control of body growth via hypothalamus/pituitary secretions (12,13), they currently lack empirical support, whilst interspecific transplantation experiments in birds (14) suggest body size does not control brain growth. This suggests the development of absolute brain size is determined independently of somatic growth.

ii) Specialisation of brain structure and development

The brain consists of individual components grouped within functionally differentiated neural systems. The extent to which these components can evolve independently of overall brain size has been keenly debated. At the extremes of this debate are the 'concerted' (Figure 1 scenario i) and 'mosaic' (Figure 1 scenario iii) models of brain evolution. The key conceptual difference between these hypotheses is the interpretation of the *cause* of allometric scaling among brain components.

The mosaic brain hypothesis (15) argues that variation in the size of individual brain components reflects adaptive divergence in brain function mediated by selection (16–19). Barton and Harvey (15) demonstrated that patterns of covariance in the volumes of mammalian brain components closely correspond to their anatomical and functional connectivity, suggesting that functional, rather than developmental, constraints cause allometric scaling between brain components. On this view, major brain components evolve together because functional systems cut across and connect them. Notably this pattern of functional co-evolution pervades biological levels and is apparent at a coarse level of component volumes (15,20) as well as at the levels of sub-component volumes (21,22) and cellular composition (23).

This model of brain structure evolution driven by region, or network-specific selection, is challenged by the concerted brain hypothesis that instead argues that brains evolve predominantly by global alterations to the duration of neurogenesis, increasing or decreasing all components together (24,25). This model of brain evolution explains allometries between brain components as the product of a highly conserved order of neurogenesis, with structures completing neurogenesis late in development (such as the neocortex) growing disproportionately large with evolutionary increases in brain size. This hypothesis has important implications as it suggests a reduced or simpler role for selection in shaping brain structure,

emphasizing the role of constraints on brain structure based on developmental conservatism. The mosaic hypothesis does not rule out such developmental integration, but suggests that where it is present it will be the product of selection to maintain functional correspondences (15).

These models are not mutually exclusive, but their relative contributions to variation in brain structure are debated. Discriminating between alternative sources of evolutionary constraint using only comparative volumetric data from adults is challenging as similar patterns of co-variation among major brain components could be produced by alternative mechanism (Figure 1). The two hypotheses can however be discriminated at the level of functional systems. A common misconception of the mosaic hypothesis is that it explains only a small proportion of variation, i.e. the residual variation that persists after accounting for overall brain size (25). However, the hypothesis is not that mosaic evolution shapes residual volumes of individual components *per se*, but that it shapes functional systems as a whole. Selection on such systems cause functionally connected components to evolve in a coordinated fashion such that patterns of co-variation reflect functional, rather than developmental constraints (Figure 1 scenarios iv, v). The mosaic hypothesis also explains features of brain evolution that are not predicted under a model emphasizing conserved developmental programs including i) the presence of partial correlations among individual components that correspond to functional connections and which are similar, but not identical, in different phylogenetic groups (15,20,21); ii) evidence that individual components of neural systems can deviate from an general pattern of correlated evolution (15,21); and iii) interspecific variation in component size more strongly correlated with ecology than with overall brain size (reviewed and critiqued in 27). These observations suggest patterns of co-variance between components can themselves evolve in response to changes in selection pressure.

Discriminating selection from constraint: new approaches to open questions

These evolutionary models of brain size and structure make contrasting predictions about the causes and consequences of the scaling relationships that can be tested by studying the cellular basis of volumetric variation and by dissecting the genetic causes of phenotypic variation. The concerted model suggests the majority of variance in a component size will be explained by a genetic correlation with total brain size, whilst the mosaic model predicts more independent genetic bases for discrete traits.

Revealing the proximate bases of brain evolution therefore has the potential to resolve questions regarding the capacity for selection to act on the brain:

- Is co-evolution due to selective co-variance, resulting from selection acting independently on multiple traits, or pleiotropy?
- Can selection act on loci with specific effects on individual components?
- How frequently, when and why, does selection act on loci with global effects relative to loci with local effects?
- Does selective co-variance drive the evolution of integrated development?

Here, focusing on vertebrate brain evolution, we identify converging insights from multiple fields to discuss the causes and consequences of tissue scaling in brain evolution.

1) Selective decoupling of co-evolving traits

Inter-specific variation provides straightforward evidence that brain components can vary in size independently of one another. This literature is reviewed and critiqued elsewhere (28), here we instead focus on new data from comparisons *within* species, both under artificial selection and in wild populations, and what these reveal about genetic correlations between brain traits. Artificial selection studies provided the initial empirical evidence for genetic covariance between brain and body size by demonstrating a concurrent response in brain size when selecting for body size (29–31). However, additional experiments have demonstrated that artificial selection can alter relative brain size through specific changes in brain volume (32). These results are supported by data from domesticated animals, themselves the products of long-term artificial selection. Compared to their wild ancestors, several domesticated species show major grade-shift in allometric scaling between brain and body mass, caused by a specific reduction in brain mass (33). This capacity for a decoupling of brain and body size evolution is further bolstered by comparative studies that show these traits can evolve with distinct evolutionary patterns over long time periods (34–38). Importantly, some of these cases indicate specific selection on brain mass, not body mass (35,38).

Similarly, selection experiments for specific motor behaviours have been demonstrated to have a targeted effect on midbrain volume, independently of other brain regions (39). Domesticated brains also show divergence in brain structure, with

differential contraction, and sometimes expansion of individual brain components (33). The expansion of the hippocampus in homing pigeons (*Columbia livia*) (40), and selective decrease in the size of the lateral geniculate nucleus of domestic compared to Spanish wild cats (41) provide notable examples of this effect.

Until relatively recently there were few examples of how wild populations respond to contrasting selection pressures on brain morphology on a micro-evolutionary time scale (42). This has begun to change, with several studies examining evidence of local adaptation between recently diverged populations. These have identified mosaic patterns of brain evolution at a micro-evolutionary scale. Inter-population differences in brain architecture, associated with environmental or behavioural variation, have been reported to affect telencephalon, optic tectum, and cerebellum size in nine-spine sticklebacks (*Pungitius pungitius*) (43), telencephalon morphology in three-spine sticklebacks (*Gasterosteus aculeatus*) (44), and cerebellum size in migratory brown trout (*Salmo trutta*) (45), independently of overall brain size. These suggest conclusions derived from the products of artificial selection are not aberrant but may accurately reflect the evolvability of brain structure.

2) Genetic architecture of brain structure within species

Quantitative genetics provides a more direct approach to assess the genetic architecture underpinning variation in brain size and structure within species. It allows an investigation of how many genomic regions control phenotypic variation, and whether phenotypic covariation in distinct traits reflects underlying genetic correlations (i.e. a common genetic basis) that imply the presence of pleiotropic effects, where variation in one gene affects multiple traits.

Selection experiments in rodents that reported a significant response in body mass when selection acted on brain mass (29–31) were influential in interpreting patterns of brain:body allometry despite the fact that the reported genetic correlations are not high enough to reflect strong constraints (46). Indeed, in some strains there is no significant covariance between brain and body size (47) and the rank-order correlation between brain and body mass across strains is not significant (48). These results imply some degree of genetic independence. This conclusion has been supported by genome-wide mapping of quantitative trait loci that suggest there is little or no genetic covariance between either brain and body size, or between sub-components of the brain (49). Overall volume and neuron number of individual sub-

components may also have independent genetic bases (50,51), implying that developmental models tying one to the other will have limited predictive power. Evidence for genetic independence between brain components has also been reported in sticklebacks and between chicken breeds (52,53). In sticklebacks, genetic correlations between brain components are significantly less than unity, despite a relatively high correlation between brain and body size (52). This suggests that even where body size does constrain the evolution of brain size, brain structure may still undergo adaptive reorganization.

Phenotypic variation in populations or colonies of free ranging primates mirror this pattern of genetic independence between brain traits. Structural traits in the brains of multiple primate species show evidence of independence both at the level of whole brain component volume and in different traits of a single component (54–56). Where they exist, patterns of genetic co-variance may even suggest counter-intuitive patterns of covariance. For example, Rogers et al. (56) report a *negative* genetic correlation between cerebral volume and gyrification in both *Papio* and humans despite their *positive* evolutionary relationship during primate brain evolution (57, but see 58). Anatomical co-variation (59) and genome-wide association studies in humans provide further evidence of independence in brain component variability (60,61). Quantitative genetic analysis of brain size and structure in different species are therefore largely in agreement: although much is still to learn about the genetic architecture of brain structure, the hypothesis that widespread genetic constraints restrict patterns of independent variation is not currently supported.

3) Molecular divergence and brain structure across species

Increased availability of molecular data has led to the identification of loci that contribute to species differences in brain size or structure. The functional effects of these genes provide an initial assessment of whether selection acts on local or global phenotypes in the brain across longer evolutionary periods. Some of these loci appear to affect brain size independently of body size. For example, two genes associated with human micrococephaly, *ASPM* and *CDK5RAP2*, show signatures of co-evolution with brain mass, but not body mass (9,62). Sequence variation in several microcephaly genes has also been associated with variation in human brain volume (63,64). *ASPM* and *CDK5RAP2* regulate proliferative divisions of neural progenitor cells during early brain development (65). This, and the relatively conserved brain

architecture of individuals with microcephaly (66) and *ASPM* knock-out mice (67), may suggest they act to delay the time schedule of neurogenesis (42). Selection on genetic variation with this effect could conceivably cause a concerted pattern of brain evolution. A similar developmental change may underpin the response to artificial selection on brain size in guppies (*Poecilia reticulata*) (32) which is associated with the changes in the expression level of *Ang-1* (68). *Ang-1* regulates the neurogenic output of neural progenitor cells (69) and its increased expression may promote a general expansion in brain size.

Elsewhere however, there is evidence that selection has shaped the evolution of genes with more specific, localised developmental effects. *Nin*, for example, is implicated in the prolonged neurogenic output of cortical neural progenitors (70) and evolved adaptively in primates in association with variation in the number of neurons per unit area of cortex (71). Several further loci with human-specific accelerated rates of evolution (72,73), loss of function (74), or duplication (75) are implicated in evolutionary changes specific to the developing forebrain. For example, the rapid evolution of an enhancer, *HARE5*, drives an upregulation of *FZD8* expression specific to the lateral telencephalon, resulting in a greater neurogenic output during corticogenesis (73). Another enhancer, *HAR142*, with a human-specific acceleration in substitution rate alters the expression of *NPAS3*, a transcription factor implicated in forebrain development (72). Human-specific loss of a conserved regulatory region near *GADD45G*, drives region-specific expression and cell-cycle dynamics in the sub-ventricular zone of the preoptic area, thalamus and hypothalamus (74). Finally, a Rho GTPase activating gene, *ARHGAP11B*, the product of a duplication event on the terminal human lineage, promotes self-renewal of radial glial cells during cortical neurogenesis (75).

A further suite of loci with human-specific patterns of molecular evolution appear to alter the regulation of neurite outgrowth and wiring (76,77). The developmental effects of inter-specific variation in these genes appear to act on specific areas of the developing brain. The most well studied example of this is the role of *FOXP2* in speech development and evolution (76). Human *FOXP2* has two derived amino acid substitutions that specifically alter dopamine concentrations, dendrite length and synaptic plasticity in the basal ganglia of a transgenic mouse model (76), and purkinje cell function in the cerebellum (78). Differential expression of another FOX family gene, *FOXP1*, in the avian telencephalon also provides support for the region-specific

action of key transcription factors in moderating mosaic patterns of brain evolution (79). The human-specific duplication of *SRGAP2* provides a further example of localised effects, in which antagonistic interactions between the duplicated copies result in altered expression profiles that affect dendritic morphology during neocortical maturation (77,80). Together, these results underline the capacity for selection to act on genetic variants that effect distinct neurodevelopmental processes to modify fine details of brain structure, supporting mosaic evolution within and between brain components.

4) Volumetric data may disguise hidden diversity: insights from cellular scaling

The concerted model of brain evolution specifies that late developing structures (notably the neocortex) grow disproportionately large during episodes of brain expansion (24,25,81). This is argued to occur as a result of increased rounds of neurogenesis produced by an overall extension of the period of development. Since the volume allometries among brain structures are postulated to be driven by differing production of neurons, according to this model the proportion of total brain volume a component occupies should be closely related to the proportion of total neuron number dedicated to that structure. For example, the neocortex should not only be disproportionately large in large-brained species, but also contain a disproportionately large number of neurons. Recent data in fact suggest volumetric and neuron number proportions are uncorrelated; the ratio between neuron numbers in neocortex and cerebellum is relatively constant, despite the substantial cross-species variation in the ratio between their volumes (82–84). Within the neocortex, frontal regions become disproportionately large as overall brain size increases, but this is not matched by a disproportionate increase in neuron numbers, because neuron density declines more steeply in frontal than in posterior cortex (84). This suggests that volumetric allometries reflect a trade-off between volume and neuron densities, with steeper declines in frontal neuron density with increasing overall size compensated by steeper increases in volume.

This pattern is not predicted by the “late equals large” hypothesis associated with the concerted model of brain expansion (24,25). Under this hypothesis, late maturing structures grow relatively larger in large brains because they acquire relatively more neurons due to increased duration of neurogenesis (see Figure 4 in 25). Charvet et al (85) suggest that the rostro-caudal gradient in cortical neuron

density, and the fact that this gradient is steeper in large-brained species, matches the predictions of the "late equals large hypothesis", as late-maturing caudal cortex has higher neuron densities. Yet, the volumetric allometry is the opposite to the pattern predicted; as brain size increases the caudal cortex becomes smaller as a proportion of cortical size, whilst the rostral cortex becomes larger. Furthermore, a striking feature of these data is the substantially higher number of cortical neurons in primate brains than in rodent brains of similar size (82), a pattern consistent with mosaic increase in cortical size in primates (15) and not with a general allometric rule relating cortical neuron numbers to brain size (24,25), or with the claim that numbers of neurons in a structure "is very highly predictable in allometric scaling of whole brain size" (86).

Further data on the cellular composition and neuron density of mammalian brains demonstrate several clade-specific shifts in the relationship between volume and neuron number (82), consistent with evidence these traits have distinct genetic bases (50,51). The apparent similarity in volumetric scaling relationships of different brain structures across mammals (24), which has itself been challenged (87), does not reflect uniformity in neuron number (83,85). This runs counter to the hypothesis that developmental programs of neurogenesis are widely and strongly conserved (25,88). Instead, it suggests that meaningful variation in timing or rate of brain development exists (89). These developmental mechanisms must facilitate region-specific alterations in the development of neuron number.

5) Developmental models of mosaic evolution

If the size of brain components can evolve independently it is important to question how these mosaic changes occur, and how size is regulated at a local level. Recent data suggest ways three, potentially non-mutually exclusive, ways mosaic evolution can be achieved (Figure 2): i) shifts in fate-determining signals, ii) region-specific delays in the schedule of neurogenesis, iii) variation in cell-cycle rates.

Shifts in the boundaries of expression profiles of fate-determining signals can alter what proportions of neural progenitors are assigned to each brain region. This effect has been demonstrated between closely related, but ecologically divergent species of *Astyanax* cavefish and African cichlids (90,91), and may contribute to other examples of mosaic brain evolution (92,93). In *Astyanax* changes in the expression domains of a secreted morphogen, *Shh*, produce putatively adaptive region-specific changes in multiple brain regions, in particular, hypothalamus size (90). In African

cichlids, species-differences in morphogen patterning along the anterior-posterior brain axis cause specific, differential expansion of the telencephalon (91).

Interspecific variation in the schedule and timing of neurogenesis provides an alternative route to region-specific expansion. Telencephalon expansion in Passerimorphae (parrots and passerine birds) is caused by a specific delay in telencephalic neurogenesis (92,94,95) that drives an increase in the number of progenitor cells destined for the telencephalon. This delay is accompanied by the emergence of a 'sub-ventricular zone' (95), analogous to that observed in large brained mammals which is thought to underpin cortical expansion (96). A similar mechanism may facilitate the expansion of the retina in a nocturnal owl monkeys (*Aotus azarae*) (97).

Despite an ever-increasing understanding of the mechanisms of cell division, how cell proliferation is controlled to produce the correct number of neurons remains an ill answered question and one of central importance to understanding how tissue size is regulated and constrained. For example, global regulation of the duration and rate of cell proliferation are likely to produce concerted patterns of brain expansion, whilst local control of proliferation would instead facilitate mosaic patterns of evolution. Recently, Buzi et al. (98) demonstrated the potential for descendent cells to regulate the duration of proliferative division in their own progenitor pools through "integral feedback" mediated by secreted molecules. Under this model the strength of an inhibitive signal on cell division increases as descendent cells accumulate until it causes a cessation of proliferation. Notably, this is only a stable size-determining system in cell lineages with intermediate cells and lineage branching, as is the case in neurogenesis (99). In other tissues, members of the TGF-β gene family, which have known roles in cell differentiation (100) and brain development (101), function as the signal molecule. TGF-β signals are only effective across small spatial scales suggesting local feedback operates at a tissue-specific rather than whole organ level (98). It is an intriguing hypothesis that modification of such signals would allow local control and variation in cell proliferation, facilitating mosaic evolution.

Accelerating the cell-cycle rate within a conserved time schedule provides an alternative route to region-specific changes in neuron number (102). In galliform birds a short period of accelerated cell cycling before the onset of neurogenesis can explain much of the variance in brain size between chickens and bobwhite quail (94,103). The cell cycle of cortical precursors is longer in primates than in rodents, which also differ

in the relative size of proliferative and post-mitotic compartments, and the presence of sub-populations of cell types. (104). This provides a potential developmental mechanism for the relative expansion of the primate cortex, indeed, fixed differences in several genes linked to human brain expansion accelerate cell cycle rates (73,74).

Although aspects of the schedule of neurogenesis may be partly conserved (24,25,105) this does not appear to represent a consistent prohibitive constraint to region specific divergence, when favoured by selection. Variation in the timing of neurogenesis, cell cycle rates, and patterning of progenitor pools suggest these processes can, at least in part, evolve independently (106), offering alternative routes through which selection can act. These three routes to the diversification of brain structure may take effect at different stages of development. For example, a purely concerted model of brain evolution posits variation along a conserved developmental schedule. This should predict that the growth curves of different brain regions are similar across species with contrasting total brain sizes. In contrast, variation in the gene expression patterns that determine brain modularity may effect early development, meaning the relative expansion or contraction of brain components should be observed once boundaries between structures are established causing a grade-shift in the growth curve of brain components (107). Volumetric variation caused by region-specific changes in the duration or cell cycle rate of neurogenesis may instead only become manifest later in development, with an initially conserved architecture giving way to greater interspecific variation as development progresses, associated with variation in the slope of the growth curve.

Comparative analysis of component growth may provide a quantitative approach to assess the frequency of different developmental mechanisms once sufficient data is available. Existing models that take such an approach are, unfortunately, derived from a relatively small (n = 18) and incomplete dataset of developmental events in mammals (25,105,108). Despite supporting a largely concerted view of brain evolution (25,105,108), the model also reveals notable examples of taxon-specific heterochrony and the raw data suggest correlations between developmental events across species are often only moderate or even non-significant (see associated commentary on 25), implying the capacity for selection to produce interspecific variation at multiple developmental time points.

Future directions: the genetic toolbox for comparative neuroanatomy

In recent years new data from disparate fields of experimental evolution, comparative biology, quantitative and molecular genetics, and development together demonstrate the presence of independent variation in separate components of brain systems, and the ability of selection to act upon it. The emergence of new techniques in these fields should continue to accelerate our understanding of the causes of tissue scaling. Large, high quality phenotypic datasets (82,109), comparative methods to detect selection on phenotypes (110), and new sequencing methods that increase the power of quantitative genetics (49,52,53) and permit phylogenetic tests of gene-phenotype associations, will allow us to examine how patterns of genetic correlations observed within species persist at a macro-evolutionary scale and test hypotheses about how brains evolve. These advances can be combined to facilitate novel insights into the influence of functional and developmental constraint on brain evolution. For example:

1. How does selection negotiate or re-shape genetic correlations between components? By coupling quantitative genetics with selection experiments favouring expansion of total brain size, an individual component or a pair of components, the genetic architecture before and after a selection event could be assessed. This would permit an examination of whether genetic correlations channel and constrain brain evolution, or whether selection can re-shape or produce genetic integration between brain components. For example, if the response of multiple components is due to a common developmental shift variation in the size of these structures should show significant genetic correlations (e.g. Figure 1i), if they do not this may suggest secondary selection on independent loci to maintain functional associations (e.g. Figure 1v).
2. What explains the presence of genetic correlations? Where present, the strength of genetic correlations between components could be combined with data on developmental (or evolutionary) origin and connectivity, to test whether genetic correlations evolve in response to functional integration (Figure 1v), or reflect patterns of conserved developmental origin (Figure 1i).
3. Do genes targeted by selection have local (Figure 1iii) or global (Figure 1i) developmental effects? The continued pursuit of genes regulating species differences in brain size and structure will provide a direct assessment of whether the evolution of separate brain components can be shaped by

selection independently of total brains size through functional assays of the effects of variation in candidate gene sequence or regulation.

4. Does selective expansion of peripheral sensory structures cause a concerted expansion of connected central structures as a result of activity-dependent development? By identifying genes with specific effects on neural development of peripheral structures, functional analyses could examine how increased input to connected structures alter their development (e.g. 110). These functional associations could conceivably drive the concerted evolution of connected brain regions if projection neurons or morphogens originating from peripheral structures influence patterns of growth in related brain regions (resulting in scenario vi in Figure 1).
5. Do differences in the relationship between volume and neuron number across brain structures, and across mammalian clades, reflect differences in the duration or rate of cell division among neural progenitors? Comparative development of species representing alternative scaling relationships can be used to test models of mosaic evolution.
6. Did the human brain evolve by an extension or exaggeration of conserved genetic and developmental processes that shape variation in brain size and structure across primates? And to what extent is human brain expansion the product of unique neurodevelopmental changes? Functional analysis of the developmental and physiological effect of genes targeted by selection during independent episodes of brain expansion may reveal functional variation in adaptive neural traits.

A greater understanding of the causes of covariance and co-evolution between brain components will in turn further our understanding of how brains adapt to changing selection pressures. The relative importance of concerted and mosaic brain evolution may vary across time and taxa, dependent on the selection pressures acting on brain size and structure. Understanding the circumstances under which selection favours alternative route of phenotypic evolution is a significant challenge, but will be central to understanding how brains evolve.

Acknowledgements

SHM is funded by a Leverhulme Trust Early Career Fellowship. We thank Peter Harrison and Trevor Price for helpful discussion.

References NEED TIDYING

1. White J, Gould S. Interpretation of the coefficient in the allometric equation. Am Nat. 1965;99(904):5–18.

2. Gould SJ. Allometry and size in ontogeny and phylogeny. Biol Rev Camb Philos Soc. 1966;41:587–640.

3. Jerison H. Evolution of the Brain and Intelligence. New York: Academic Press; 1973.

4. Dubois E. Sur le rapport de l' encephale avec la grandeur du corps chez les Mammiferes. Bull Soc Anthr Paris. 1897;4(8):337–74.

5. Aboitiz F. Does bigger mean better? Evolutionary determinants of brain size and structure. Brain Behav Evol. 1996;47:225–45.

6. Atchley WR. Developmental Quantitative Genetics and the Evolution of Ontogenies. Evolution (N Y). 1987;41(2):316–30.

7. Barton R a, Capellini I. Maternal investment, life histories, and the costs of brain growth in mammals. Proc Natl Acad Sci U S A. 2011;108(21):6169–74.

8. Montgomery SH, Capellini I, Barton RA, Mundy NI. Reconstructing the ups and downs of primate brain evolution: implications for adaptive hypotheses and Homo floresiensis. BMC Biol. 2010;8:9.

9. Montgomery SH, Capellini I, Venditti C, Barton RA, Mundy NI. Adaptive evolution of four microcephaly genes and the evolution of brain size in anthropoid primates. Mol Biol Evol. 2011;28(1):625–38.

10. Ngwenya A, Patzke N, Spocter MA, Kruger JL, Dell LA, Chawana R, et al. The continuously growing central nervous system of the nile crocodile (Crocodylus niloticus). Anat Rec. 2013;296(10):1489–500.

11. Williams RW, Herrup K. The control of neuron number. Annu Rev Neurosci.

1988;11:423–53.

12. Tannenbaum GS, Guyda HJ, Posner BI. Insulin-like growth factors: a role in growth hormone negative feedback and body weight regulation via brain. Science (80-). 1983;220(4592):77–9.

13. Deacon TW. Problems of ontogeny and phylogeny in brain-size evolution. Int J Primatol. 1990;11(3):237–82.

14. Balaban E, Teillet M, Le Douarin N. Application of the quil-chick chimera system to the study of brain development and behaviour. Science (80-). 1988;241:1339–42.

15. Barton R a, Harvey PH. Mosaic evolution of brain structure in mammals. Nature [Internet]. 2000 Jun 29;405(6790):1055–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10890446

16. Eisenberg J. The mammalian radiations: an analysis of trends in evolution, adaptation, and behavior. Chicago: University of Chicago Press; 1981.

17. Stephan H, Frahm H, Baron G. New and Revised Data on Volumes of Brain Structures in Insectivores and Primates. Folia Primatol [Internet]. Karger Publishers; 1981 [cited 2014 Apr 10];35(1):1–29. Available from: http://www.karger.com/Article/FullText/155963

18. Harvey PH, Krebs J. Comparing brains. Science (80-). 1990;249(4965):140–6.

19. de Winter W, Oxnard CE. Evolutionary radiations and convergences in the structural organization of mammalian brains. Nature [Internet]. 2001 Feb 8;409(6821):710–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11217859

20. Iwaniuk AN, Dean KM, Nelson JE. A mosaic pattern characterizes the evolution of the avian brain. Proc Biol Sci [Internet]. 2004 May 7 [cited 2014 Apr 8];271 Suppl (Suppl_4):S148–51. Available from: http://rspb.royalsocietypublishing.org/content/271/Suppl_4/S148.short

21. Whiting B a., Barton R a. The evolution of the cortico-cerebellar complex in primates: Anatomical connections predict patterns of correlated evolution. J

552 Hum Evol. 2003;44:3–10.

553 22. Barton R a. Evolutionary specialization in mammalian cortical structure. J Evol
554 Biol. 2007;20:1504–11.

555 23. Lewitus E, Hof PR, Sherwood CC. Phylogenetic comparison of neuron and glia
556 densities in the primary visual cortex and hippocampus of carnivores and
557 primates. Evolution (N Y). 2012;66(Voogd 2003):2551–63.

558 24. Finlay B, Darlington R. Linked regularities in the development and evolution
559 of mammalian brains. Science (80-) [Internet]. 1995 Jun 16 [cited 2014 Apr
560 10];268(5217):1578–84. Available from:
561 http://www.sciencemag.org/content/268/5217/1578.abstract

562 25. Finlay BL, Darlington RB, Nicastro N. Developmental structure in brain
563 evolution. Behav Brain Sci. 2001;24:263–78; discussion 278–308.

564 26. Barton R a, Venditti C. Report Rapid Evolution of the Cerebellum in Humans
565 and Other Great Apes. Curr Biol [Internet]. Elsevier Ltd; 2014;24(20):2440–4.
566 Available from: http://dx.doi.org/10.1016/j.cub.2014.08.056

567 27. Healy SD, Rowe C. A critique of comparative studies of brain size. Proc R Soc
568 B Biol Sci [Internet]. 2007 Feb 22 [cited 2014 Mar 19];274(1609):453–64.
569 Available from:
570 http://rspb.royalsocietypublishing.org/content/274/1609/453.short

571 28. Healy SD, Rowe C. A critique of comparative studies of brain size. Proc R Soc
572 B-Biological Sci [Internet]. 2007;274(1609):453–64. Available from:
573 http://rspb.royalsocietypublishing.org/cgi/doi/10.1098/rspb.2006.3748

574 29. Fuller J, Geils H. Brain growth in mice selected for high and low brain weight.
575 Dev Psychobiol. 1972;5(4):307–18.

576 30. Atchley WR. The effect of selection on brain and body size association in rats.
577 Genet Res. 1984;43:289–98.

578 31. Atchley WR, Riska B, Kohn LAP, Plummer AA. A quantitative genetic
579 analysis of brain and body size associations. Their origin and ontogeny: Data
580 from mice. Evolution. 1984;38(6):1165–79.

581 32. Kotrschal A, Rogell B, Bundsen A, Svensson B, Zajitschek S, Brännström I, et
582 al. Artificial selection on relative brain size in the guppy reveals costs and
583 benefits of evolving a larger brain. Curr Biol. 2013;23:168–71.

584 33. Kruska DCT. On the evolutionary significance of encephalization in some
585 eutherian mammals: Effects of adaptive radiation, domestication, and
586 feralization. Brain Behav Evol. 2005;65:73–108.

587 34. Gonzalez-Voyer A, Winberg S, Kolm N. Distinct evolutionary patterns of brain
588 and body size during adaptive radiation. Evolution (N Y). 2009;63:2266–74.

589 35. Montgomery SH, Capellini I, Barton R a, Mundy NI. Reconstructing the ups
590 and downs of primate brain evolution: implications for adaptive hypotheses and
591 Homo floresiensis. BMC Biol. 2010;8:9.

592 36. Montgomery SH, Geisler JH, McGowen MR, Fox C, Marino L, Gatesy J. The
593 evolutionary history of cetacean brain and body size. Evolution (N Y)
594 [Internet]. 2013;n/a – n/a. Available from:
595 http://doi.wiley.com/10.1111/evo.12197

596 37. Fitzpatrick JL, Almbro M, Gonzalez-Voyer a., Hamada S, Pennington C,
597 Scanlan J, et al. Sexual selection uncouples the evolution of brain and body
598 size in pinnipeds. J Evol Biol. 2012;25:1321–30.

599 38. Finarelli J a, Flynn JJ. Brain-size evolution and sociality in Carnivora. Proc
600 Natl Acad Sci U S A. 2009;106(23):9345–9.

601 39. Kolb EM, Rezende EL, Holness L, Radtke a, Lee SK, Obenaus a, et al. Mice
602 selectively bred for high voluntary wheel running have larger midbrains:
603 support for the mosaic model of brain evolution. J Exp Biol [Internet].
604 2013;216:515–23. Available from:
605 http://www.ncbi.nlm.nih.gov/pubmed/23325861

606 40. Rehkämper G, Frahm HD, Cnotka J. Mosaic evolution and adaptive brain
607 component alteration under domestication seen on the background of
608 evolutionary theory. Brain Behav Evol. 2008;71:115–26.

609 41. Williams RW, Cavada C, Reinoso-Suárez F. Rapid evolution of the visual

system: a cellular assay of the retina and dorsal lateral geniculate nucleus of the Spanish wildcat and the domestic cat. J Neurosci. 1993;13(1):208–28.

42. Striedter GF. Principles of brain evolution. Sinauer Associates; 2005.

43. Gonda A, Herczeg G, Merilä J. Population variation in brain size of nine-spined sticklebacks (Pungitius pungitius)--local adaptation or environmentally induced variation? BMC Evol Biol [Internet]. BioMed Central Ltd; 2011;11(1):75. Available from: http://www.biomedcentral.com/1471-2148/11/75

44. Park PJ, Bell M a. Variation of telencephalon morphology of the threespine stickleback (Gasterosteus aculeatus) in relation to inferred ecology. J Evol Biol. 2010;23:1261–77.

45. Kolm N, Gonzalez-Voyer a., Brelin D, Winberg S. Evidence for small scale variation in the vertebrate brain: Mating strategy and sex affect brain size and structure in wild brown trout (Salmo trutta). J Evol Biol. 2009;22:2524–31.

46. Lande R. Quantitative Genetic Analysis of Multivariate Evolution , Applied to Brain : Body Size Allometry Russell Lande. Evolution (N Y). 1979;33(1):402–16.

47. Belknap JK, Phillips TJ, O'Toole L a. Quantitative trait loci associated with brain weight in the BXD/Ty recombinant inbred mouse strains. Brain Res Bull [Internet]. 1992;29(41):337–44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1393606

48. Roderick TH, Wimer RE, Wimer CC, Schwartzkroin P a. Genetic and phenotypic variation in weight of brain and spinal cord between inbred strains of mice. Brain Res. 1973;64:345–53.

49. Hager R, Lu L, Rosen GD, Williams RW. Genetic architecture supports mosaic brain evolution and independent brain–body size regulation. Nat Commun. 2012;3(May):1079.

50. Rosen GD, Williams RW. Complex trait analysis of the mouse striatum: independent QTLs modulate volume and neuron number. BMC Neurosci.

2001;2:5.

51. Airey DC, Lu L, Williams RW. Genetic control of the mouse cerebellum: identification of quantitative trait loci modulating size and architecture. J Neurosci. 2001;21(14):5099–109.

52. Noreikiene K, Herczeg G, Gonda A, Balazs G, Husby A, Merilä J. Quantitative genetic analysis of brain size variation in sticklebacks : support for the mosaic model of brain evolution. 2015;

53. Henriksen R, Andersson L, Jensen P, Wright D. From the jungle to the barn: Independent genetic control for increased brain and body size and Mosaic brain evolution in chickens during domestication. Rev. 2015;

54. Panizzon MS, Fennema-Notestine C, Eyler LT, Jernigan TL, Prom-Wormley E, Neale M, et al. Distinct genetic influences on cortical surface area and cortical thickness. Cereb Cortex. 2009;19(Rakic 1988):2728–35.

55. Winkler AM, Kochunov P, Blangero J, Almasy L, Zilles K, Fox PT, et al. Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies. Neuroimage [Internet]. Elsevier Inc.; 2010;53(3):1135–46. Available from: http://dx.doi.org/10.1016/j.neuroimage.2009.12.028

56. Rogers J, Kochunov P, Zilles K, Shelledy W, Lancaster J, Thompson P, et al. On the genetic architecture of cortical folding and brain volume in primates. Neuroimage [Internet]. Elsevier Inc.; 2010;53(3):1103–8. Available from: http://dx.doi.org/10.1016/j.neuroimage.2010.02.020

57. Zilles K, Armstrong E, Moser KH, Schliecher A, Stephan H. Gyrification in the cerebral cortex of primates. Brain Behav Evol. 1989;34:134–50.

58. Ventura-Antunes L, Mota B, Herculano-Houzel S. Different scaling of white matter volume, cortical connectivity, and gyrification across rodent and primate brains. Front Neuroanat [Internet]. 2013;7(April):3. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3620553&tool=pmcentrez&rendertype=abstract

59. Gómez-Robles A, Hopkins WD, Sherwood CC. Modular structure facilitates mosaic evolution of the brain in chimpanzees and humans. Nat Commun [Internet]. 2014;5:4469. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25047085

60. Toro R, Poline J-B, Huguet G, Loth E, Frouin V, Banaschewski T, et al. Genomic architecture of human neuroanatomical diversity. 2013; Available from: http://biorxiv.org/lookup/doi/10.1101/001198

61. Hibar DP. Common genetic variants influence human subcortical brain structures. Nature [Internet]. Nature Publishing Group; 2015;8. Available from: http://dx.doi.org/10.1038/nature14101

62. Montgomery SH, Mundy NI. Microcephaly genes evolved adaptively throughout the evolution of eutherian mammals. BMC Evol Biol [Internet]. 2014;14(1):120. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4055943&tool=pmcentrez&rendertype=abstract

63. Rimol LM, Agartz I, Djurovic S, Brown A a, Roddey JC, Kähler AK, et al. Sex-dependent association of common variants of microcephaly genes with brain structure. Proc Natl Acad Sci U S A. 2010;107:384–8.

64. Wang JK, Li Y, Su B. A common SNP of MCPH1 is associated with cranial volume variation in Chinese population. Hum Mol Genet. 2008;17(9):1329–35.

65. Thornton GK, Woods CG. Primary microcephaly: do all roads lead to Rome? Trends Genet [Internet]. Elsevier Ltd; 2009;25(11):501–10. Available from: http://dx.doi.org/10.1016/j.tig.2009.09.011

66. Bond J, Roberts E, Mochida GH, Hampshire DJ, Scott S, Askham JM, et al. ASPM is a major determinant of cerebral cortical size. Nat Genet. 2002;32(october):316–20.

67. Pulvers JN, Bryk J, Fish JL, Wilsch-Bräuninger M, Arai Y, Schreier D, et al. Mutations in mouse Aspm (abnormal spindle-like microcephaly associated) cause not only microcephaly but also major defects in the germline. Proc Natl Acad Sci U S A. 2010;107(38):16595–600.

68. Chen Y-C, Harrison PW, Kotrschal A, Kolm N, Mank JE, Panula P. Expression change in Angiopoietin-1 underlies change in relative brain size in fish. Proc R Soc B Biol Sci. 2015;282(1810):20150872.

69. Rosa AI, Gonçalves J, Cortes L, Bernardino L, Malva JO, Agasse F. The angiogenic factor angiopoietin-1 is a proneurogenic peptide on subventricular zone stem/progenitor cells. J Neurosci. 2010;30(13):4573–84.

70. Wang X, Tsai J-W, Imai JH, Lian W-N, Vallee RB, Shi S-H. Asymmetric centrosome inheritance maintains neural progenitors in the neocortex. Nature [Internet]. Nature Publishing Group; 2009;461(7266):947–55. Available from: http://dx.doi.org/10.1038/nature08435

71. Montgomery SH, Mundy NI. Positive selection on NIN, a gene involved in neurogenesis, and primate brain evolution. Genes, Brain Behav. 2012;11(8):903–10.

72. Kamm GB, López-Leal R, Lorenzo JR, Franchini LF. A fast-evolving human NPAS3 enhancer gained reporter expression in the developing forebrain of transgenic mice. Philos Trans R Soc Lond B Biol Sci [Internet]. 2013;368(November):20130019. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24218632

73. Boyd JL, Skove SL, Rouanet JP, Pilaz L-J, Bepler T, Gordân R, et al. Human-Chimpanzee Differences in a FZD8 Enhancer Alter Cell-Cycle Dynamics in the Developing Neocortex. Curr Biol [Internet]. 2015;772–9. Available from: http://www.sciencedirect.com/science/article/pii/S0960982215000731

74. McLean CY, Reno PL, Pollen AA, Bassan AI, Capellini TD, Guenther C, et al. Human-specific loss of regulatory DNA and the evolution of human-specific traits. Nature [Internet]. Nature Publishing Group; 2011;471:216–9. Available from: http://dx.doi.org/10.1038/nature09774

75. Florio M, Albert M, Taverna E, Namba T, Brandl H, Lewitus E, et al. Human-specific gene ARHGAP11B promotes basal progenitor amplification and neocortex expansion. Science. 2015;347(6229):1465–70.

76. Enard W, Gehre S, Hammerschmidt K, Hölter SM, Blass T, Somel M, et al. A

728 Humanized Version of Foxp2 Affects Cortico-Basal Ganglia Circuits in Mice.
729 Cell. 2009;137:961–71.

730 77. Charrier C, Joshi K, Coutinho-Budd J, Kim JE, Lambert N, De Marchena J, et
731 al. Inhibition of SRGAP2 function by its human-specific paralogs induces
732 neoteny during spine maturation. Cell. 2012;149:923–35.

733 78. Fujita-jimbo E, Momoi T. Neuroscience Letters Specific expression of FOXP2
734 in cerebellum improves ultrasonic vocalization in heterozygous but not in
735 homozygous Foxp2 (R552H) knock-in pups. Neurosci Lett [Internet]. Elsevier
736 Ireland Ltd; 2014;566:162–6. Available from:
737 http://dx.doi.org/10.1016/j.neulet.2014.02.062

738 79. Garcia-Calero E, Martinez S. FoxP1 Protein Shows Differential Layer
739 Expression in the Parahippocampal Domain among Bird Species. 2016;

740 80. Dennis MY, Nuttle X, Sudmant PH, Antonacci F, Graves T a., Nefedov M, et
741 al. Evolution of human-specific neural SRGAP2 genes by incomplete
742 segmental duplication. Cell [Internet]. Elsevier Inc.; 2012;149(4):912–22.
743 Available from: http://dx.doi.org/10.1016/j.cell.2012.03.033

744 81. Finlay BL, Clancy B, Darlington RB. Late still equals large. Brain Behav Evol.
745 2010;75:4–6.

746 82. Herculano-Houzel S. Not all brains are made the same: New views on brain
747 scaling in evolution. Brain Behav Evol. 2011;78:22–36.

748 83. Herculano-Houzel S, Manger PR, Kaas JH. Brain scaling in mammalian
749 evolution as a consequence of concerted and mosaic changes in numbers of
750 neurons and average neuronal cell size. Front Neuroanat [Internet]. 2014;8.
751 Available from:
752 http://www.frontiersin.org/Neuroanatomy/10.3389/fnana.2014.00077/abstract

753 84. Barton R a. Embodied cognitive evolution and the cerebellum. 2012;2097–107.
754 Available from: http://dx.doi.org/10.1098/rstb.2012.0112

755 85. Charvet CJ, Cahalane DJ, Finlay BL. Systematic, cross-cortex variation in
756 neuron numbers in rodents and primates. Cereb Cortex. 2015;25(1):147–60.

86. Anderson ML, Finlay BL. Allocating structure to function: the strong links between neuroplasticity and natural selection. Front Hum Neurosci [Internet]. 2013;7(January):918. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3882658&tool=pmcentrez&rendertype=abstract

87. Willemet R. Understanding the Evolution of Mammalian Brain Structures; the Need for a (New) Cerebrotype Approach. 2012;203–24.

88. Charvet CJ, Finlay BL. Embrcing covariation in brain evolution : Large brains, extended development, and flexible primate social systems. Prog Brain Res. 2012;195(607):71–87.

89. Weisbecker V. Why "late equals large" does not work. Neuroscience [Internet]. Elsevier Inc.; 2009;164(4):1648–52. Available from: http://dx.doi.org/10.1016/j.neuroscience.2009.09.027

90. Menuet A, Alunni A, Joly J-S, Jeffery WR, Rétaux S. Expanded expression of Sonic Hedgehog in Astyanax cavefish: multiple consequences on forebrain development and evolution. Development. 2007;134:845–55.

91. Sylvester JB, Rich C a, Loh Y-HE, van Staaden MJ, Fraser GJ, Streelman JT. Brain diversity evolves via differences in patterning. Proc Natl Acad Sci U S A. 2010;107:9718–23.

92. Charvet CJ, Striedter GF. Developmental origins of mosaic brain evolution: Morphometric analysis of the developing zebra finch brain. J Comp Neurol. 2009;514(December 2008):203–13.

93. Charvet CJ, Striedter GF. Developmental basis for telencephalon expansion in waterfowl: enlargement prior to neurogenesis. Proc Biol Sci. 2009;276:3421–7.

94. Striedter GF, Charvet CJ. Developmental origins of species differences in telencephalon and tectum size: Morphometric comparisons between a parakeet (Melopsittacus undulatus) and a quail (Colinus virgianus). J Comp Neurol. 2008;507(December 2007):1663–75.

95. Striedter GF, Charvet CJ. Telencephalon enlargement by the convergent

786 evolution of expanded subventricular zones. Biol Lett. 2009;5(October
787 2008):134–7.

788 96. Lewitus E, Kelava I, Kalinka AT, Tomancak P, Huttner WB. An Adaptive
789 Threshold in Mammalian Neocortical Evolution. 2013;12(11):38. Available
790 from:
791 http://arxiv.org/abs/1304.5412\nhttp://biorxiv.org/lookup/doi/10.1101/001289

792 97. Dyer MA, Martins R, Filho S, Muniz APC, Carlos L, Silveira L, et al.
793 Developmental sources of conservation and variation in the evolution of the
794 primate eye. 2009;106(22):8963–8.

795 98. Buzi G, Lander AD, Khammash M. Cell lineage branching as a strategy for
796 proliferative control. BMC Biol [Internet]. 2015;13. Available from:
797 http://www.biomedcentral.com/1741-7007/13/13

798 99. Götz M, Huttner WB. The cell biology of neurogenesis. Nat Rev Mol Cell
799 Biol. 2005;6:777–88.

800 100. Kitisin K, Ganesan N, Tang Y, Jogunoori W, Volpe E a, Kim SS, et al.
801 Disruption of transforming growth factor-beta signaling through beta-spectrin
802 ELF leads to hepatocellular cancer through cyclin D1 activation. Oncogene.
803 2007;26(December 2006):7103–10.

804 101. Gámez B, Rodriguez-Carballo E, Ventura F. BMP signaling in telencephalic
805 neural cell specification and maturation. Front Cell Neurosci [Internet].
806 2013;7(June):87. Available from:
807 http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3671186&tool=pm
808 centrez&rendertype=abstract

809 102. Kornack DR, Rakic P. Changes in cell-cycle kinetics during the development
810 and evolution of primate neocortex. Proc Natl Acad Sci U S A.
811 1998;95(February):1242–6.

812 103. Charvet CJ, Striedter GF. Bigger brains cycle faster before neurogenesis
813 begins: a comparison of brain development between chickens and bobwhite
814 quail. Proc Biol Sci. 2010;277(June):3469–75.

104. Dehay C, Kennedy H. Cell-cycle control and cortical development. Nat Rev Neurosci. 2007;8(6):438–50.

105. Workman AD, Charvet CJ, Clancy B, Darlington RB, Finlay BL. Modeling Transformations of Neurodevelopmental Sequences across Mammalian Species. J Neurosci [Internet]. 2013;33(17):7368–83. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23616543

106. Charvet CJ, Striedter GF, Finlay BL. Evo-devo and brain scaling: Candidate developmental mechanisms for variation and constancy in vertebrate brain evolution. Brain Behav Evol. 2011;78:248–57.

107. Sylvester JB, Pottin K, Streelman JT. Integrated brain diversification along the early neuraxes. Brain Behav Evol. 2011;78(3):237–47.

108. Finlay B, Darlington R. Linked regularities in the development and evolution of mammalian brains. Science (80-) [Internet]. 1995 Jun 16 [cited 2014 Apr 10];268(5217):1578–84. Available from: http://www.sciencemag.org/content/268/5217/1578.short

109. Mars RB, Neubert F-X, Verhagen L, Sallet Jã©, Miller KL, Dunbar RIM, et al. Primate comparative neuroscience using magnetic resonance imaging: promises and challenges. Front Neurosci [Internet]. 2014;8(October):1–11. Available from: http://journal.frontiersin.org/article/10.3389/fnins.2014.00298/abstract

110. Baker J, Meade A, Pagel M, Venditti C. Positive phenotypic selection inferred from phylogenies. 2015;

111. Zembrzycki A, Stocker AM, Leinga A, Sahara S, Chou S, Kalatsky V, et al. Genetic mechanisms control the linear scaling between related cortical primary and higher order sensory areas. 2015;1–13.

FIGURES

Figure 1: Origins of evolutionary constraints and co-variance. Six scenarios that show how selection on one brain component (A) may cause coordinated changes throughout the system. The ancestral system is shown in the middle row; blue connections indicate developmental constraints (DC) and green connections indicate functional constraints (FC). Red outlines indicate the component(s) under primary selection, blue outlines indicate component(s) under secondary selection following changes in A. **i) Concerted brain evolution driven by developmental constraints:** selection on A results in concerted expansion of all brain components. **ii) Concerted evolution with a small contribution of mosaicism**: the evolution of new functions may be associated with an overall expansion of the system with a "top up" for A driven by independent developmental mechanisms (top row). **iii) Mosaic evolution:** a complete lack of constraint allows A to evolve independently. **iv) Mosaic evolution with functional constraints:** functional dependence between A and D means selection for A creates secondary selection for D to maintain the relationship between A and D (bottom row). If this functional relationship changes, A may be able to evolve without co-incident shifts in D (top row). **v) Mosaic evolution with system-wide functional dependence:** selection on A will create secondary selection on the entire system (bottom row), patterns of co-variance would appear identical to i and ii. If the functional connection changes between A and D, sub-networks A-C may evolve without co-incident shifts in A-D (top row). **vi) Mosaic evolution with partial DC and FC:** If sub-networks A/C and B/D are developmentally linked internally, but functionally linked to other sub-networks, selection on A will result in a combination of secondary selection on D to maintain their functional relationship (lower row) and concerted expansion (of C and B) due to developmental constraints; the result is identical to i, ii and v. If the functional relationship changes between A and D, A may be able to respond without co-incident shifts in B-D but will still be accompanied by a 'neutral' change in C.

Figure 2: Developmental routes to mosaic brain evolution. Selection can modify the relative size of individual brain components through three routes: A) Modifying how the progenitor pool of cells that produce neurons is divided between regions by changes the boundaries of expression gradients of morphogens. A role for developmental patterning in creating variation in brain structure between species has been demonstrated in derived, cave dwelling populations of *Atyanax mexicanus* (90) and ecologically divergent cichlids in Lake Malawi (91). B) Prolonging the period of cell division in the progenitor pool of cells destined to form a specific component. Expansion of specific brain components has been linked to interspecific variation in region-specific duration of neurogenesis in Passerimorphae (92,94,95), nocturnal *Aotus* monkeys (97) and Mammalia more generally (96). C) Accelerating the rate at which cells divide within a conserved developmental schedule. Variation in cell cycle rate prior to the onset of neurogenesis is thought to contribute to interspecific differences in the relative size of the telencephalon in galliform birds (93).