

In the light of evolution VI: Brain and behavior

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In *On the Origin of Species by Means of Natural Selection* (1859), Darwin (1) barely mentioned the brain. Only in *The Descent of Man, and Selection in Relation to Sex* (2), published in 1871, did Darwin emphasize that the human nervous system, like any other organ system, must have evolved. Even so, Darwin himself wrote little on the brain. Instead, Darwin asked his good friend T. H. Huxley to write a chapter for the second edition of *The Descent of Man, and Selection in Relation to Sex* that dealt specifically with human brain evolution. In this chapter, Huxley laid to rest Richard Owen's earlier argument that human brains are outliers among mammalian brains. Instead, Huxley argued that our brains resemble the brains of other apes in all fundamental respects. He even downplayed the greater size of human brains, noting that brain size is quite variable among humans. Importantly, Huxley did not deny that our brains must somehow differ from the brains of other apes, for he could see no other way to explain our unique cognitive capacities, most notably language. However, Huxley postulated that the differences that set our brains apart are not apparent in gross dissections (3–7).

Of course, in the days of Darwin and Huxley, the only methods available for studying large brains were gross dissections or, for functional analyses, gross brain lesions. It was only in the late 1880s that Ramón y Cajal focused neuroanatomy onto structural details by applying Golgi's famous staining method to the nervous systems of various species (8). Similarly, techniques for electrical recording of neural activity and brain stimulation were just starting to be developed in the 1870s by Richard Canton, Eduard Hitzig, and many other pioneers (9–11). Aside from these technical constraints, neurobiological knowledge was limited in Darwin's day to relatively few species. In particular, ape brains were rare in England at the time, because they could only be obtained through research expeditions to Africa. Gorillas, for example, were not even discovered by Western scientists until Richard Owen (12) described them and their brains in the late 1850s.

Since that dawn of evolutionary neuroscience, the arsenal of methods and panoply of data relevant to brain evolution have expanded tremendously. Intracellular and extracellular chronic recording techniques, immunohistochemistry, axon

tracing, and excitotoxic brain lesions are just a few of the many methods that revolutionized our understanding of brain structure and function. Obviously, neuroscience has also been transformed by molecular methods that Darwin could not have envisioned. Researchers can now compare gene sequences and gene expression patterns across species. They can also test causal hypotheses about how genes control neural development, brain function and, ultimately, behavior. Collectively, these methods make it possible to compare across species not just individual structures, such as genes or brain regions, but molecular interactions, developmental processes, and intriguing behaviors. Finally, the range of species studied by comparative neurobiologists now includes not just a few model species but a broad assemblage of vertebrates and, increasingly, invertebrates (13).

These methodological advances have unleashed a flood of data relevant to brain evolution. Fortunately, conceptual advances in data analysis kept pace. Particularly important have been breakthroughs in phylogenetic systematics, which have yielded more elaborate and detailed phylogenetic trees, or cladograms, and sophisticated statistical methods for evaluating phylogenetic correlations between various traits (14). Cladists have also developed a rigorous methodology for distinguishing similarities caused by homology from those similarities that resulted from independent evolution (15–17). With these methodologies, comparative biologists can begin to infer the evolutionary processes that created the complex tapestry of neurological systems in extant species.

Because the field of evolutionary neuroscience now includes a vast array of different approaches, data types, and species, how can one select from this diversity a set of 17 colloquium papers that represent the field adequately? The task seems Herculean, if not Sisyphean. Confronted with this challenge, we opted for an eclectic approach. Thus, we here gather 17 papers that represent a broad assortment of contemporary research in evolutionary neurobiology.

Evolutionary Origins of Neurons and Nervous Systems

The first three papers address the ancient history of neuron-related molecules and centralized nervous systems. Cecilia

Conaco et al. (18) review earlier findings that many of the molecules found in neuronal synapses, especially within the postsynaptic density, predate the evolution of neurons. The authors then use an analysis of gene coexpression patterns to show that these protosynaptic genes in sponges, which lack proper neurons, form several modules of interacting genes. With the evolution of neurons, these small modules fused into a larger module with a novel function, namely to build synapses. Thus, the research has moved beyond the relatively simple task of homologizing individual genes and begun to trace the evolution of complex and changing gene networks. An interesting, if as yet barely explored, implication of the idea that gene networks can change function is that the homologous gene networks may function in the development or function of nonhomologous structures (19). This possibility is rarely acknowledged (20).

Harold Zakon (21) reviews the evolution of voltage-gated sodium (Na^v) channels. These channels probably descended from voltage-gated calcium channels, which were probably derived from voltage-sensitive potassium channels. Why did Na^v channels become the major driving force behind neuronal action potentials? The answer is probably that because Na was plentiful in the ocean, where neurons first evolved, and because Na influx tends not to interfere with intracellular calcium signaling. Once incorporated into neurons, Na^v channels were modified in diverse, interesting ways. For example, they evolved regulatory sequences that allowed them to be clustered

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Box 1. In the light of evolution. In 1973, Dobzhansky (45) penned a short commentary titled “Nothing in biology makes sense except in the light of evolution.” Most scientists agree that evolution provides the unifying framework for interpreting biological phenomena that otherwise can often seem unrelated and perhaps unintelligible. Given the central position of evolutionary thought in biology, it is sadly ironic that evolutionary perspectives outside the sciences have often been neglected, misunderstood, or purposefully misrepresented. Biodiversity—the genetic variety of life—is an exuberant product of the evolutionary past, a vast human-supportive resource (aesthetic, intellectual, and material) of the present, and a rich legacy to cherish and preserve for the future. Two challenges as well as opportunities for 21st century science are to gain deeper insights into the evolutionary processes that foster biotic diversity and translate that understanding into workable solutions for the regional and global crises that biodiversity currently faces. A grasp of evolutionary principles and processes is important in other societal arenas as well, such as education, medicine, sociology, and other applied fields including agriculture, pharmacology, and biotechnology. The ramifications of evolutionary thought extend into learned realms traditionally reserved for philosophy and religion. The central goal of the “In the Light of Evolution” series is to promote the evolutionary sciences through state-of-the-art colloquia and their published proceedings. Each installment explores evolutionary perspectives on a particular biological topic that is scientifically intriguing but also has special relevance to contemporary societal issues or challenges. Individually and collectively, the “In the Light of Evolution” series aims to interpret phenomena in various areas of biology through the lens of evolution, address some of the most intellectually engaging as well as pragmatically important societal issues of our times, and foster a greater appreciation of evolutionary biology as a consolidating foundation for the life sciences.

at the axon initial segment and at Nodes of Ranvier in myelinated axons. Additional modifications evolved after the ancestral Na-v gene was duplicated, once near the origin of vertebrates and then again (repeatedly) in several vertebrate lineages. One of the most interesting Na-v modifications is the evolution of resistance to TTX, which typically blocks Na-v channels, in puffer fishes and other species that use TTX to ward off predators.

Glenn Northcutt (22) analyzes when and in which lineages complex brains evolved. Favoring a cladistic approach, Northcutt concludes that the last common ancestor of all bilaterian animals, living 600–700 Mya, probably had a diffusely organized nervous system. Cephalic neural ganglia apparently evolved soon thereafter and were retained in many lineages. Truly complex brains evolved even later and did so repeatedly, in mollusks, arthropods, and chordates (including vertebrates). This conclusion contrasts sharply with the conclusions of other researchers, who are struck by similarities in developmental gene expression patterns among vertebrate, insect, and annelid nervous systems. To them, these similarities must represent homologies. That is, they argue that similar gene expression patterns must have existed in the last common ancestor of fruit flies, vertebrates, and worms. Northcutt begs to differ, arguing that the expression of these genes in brains is caused by convergent evolution, perhaps

by the co-option of gene networks that predate brains. This debate will require more data for a full resolution.

Developmental and Adult Variation in Neural Organization

The five papers in this section all focus on describing and explaining variation in nervous system organization. This emphasis is important, because traditionally, comparative research tends to focus on similarities rather than differences (that is, on conservation rather than variation). However, after the conserved features are known, the research focus can shift to the nonconserved features, the variable elements. In grappling with this variation, researchers often look for constraints and scaling principles (7), and they seek to explain the variation in mechanistic terms.

Erin Jarvis et al. (23) review the segmental variation in arthropod appendages (mainly mouthparts and limbs) and its control by *hox* genes. They note that *hox* genes also control segmental variation in the motor neurons that control the various appendages. This observation is important, because it suggests that variation in *hox* gene expression patterns can coordinate evolutionary changes in appendage morphology with evolutionary changes in motor neurons, thus ensuring functionality. Pursuit of this idea will extend evo-devo (evolutionary developmental) biology, which has thus far focused primarily on body plan evolution, into the realm of

neuroscience, which is just beginning to experience an evo-devo boom (24).

Continuing the neuro-evo-devo theme, Luke McGowan et al. (25) present results from an experiment in which they used intraventricular FGF2 injections to delay neurogenesis in the optic tectum of chicks. This manipulation increases tectum size to the point where parts of the tectum form folds, an interesting finding because delays in neurogenesis have likely led to cortical folding in large-brained mammals. However, the FGF2 injections also disrupt the normally smooth pattern of tectal lamination, which is unlikely to be adaptive. Intriguingly, McGowan et al. suggest that the laminar disruptions are causally linked to ruptures in the overlying pia mater. Collectively, these findings imply that evolutionary increases in the size of brain regions must be coordinated with expansions of the associated pia mater, which may be difficult when neural expansion is caused by a delay in neurogenesis.

Leah Krubitzer and Adele Seelke (26) focus on variability in cortical organization, both within species and across mammalian taxa. In addition to describing this variability, they analyze its phylogenetic pattern and underlying mechanisms. In particular, they suggest that the cerebral cortex is constrained to vary in specific ways rather than being freely variable. This finding would explain why many features of cortical organization are broadly conserved and why some variants evolved repeatedly and independently in diverse lineages. What sorts of mechanisms generate this variation and its constraints? As Krubitzer and Seelke review, both intrinsic genetic and extrinsic activity-dependent mechanisms are at play. Furthermore, variation in one part of the nervous system can induce changes in distant, functionally related brain regions. For example, removal of the eyes during early development causes a dramatic reduction and functional respecification of the primary visual cortex. A similar cascade effect has been observed in blind mole rats. Thus, experimental manipulations of brain development can mimic at least some aspects of natural variation.

Jon Kaas (27) continues the discussion of mammalian cortical variation, but his paper is focused more explicitly on neocortical modules, which include cortical areas, patches, bands, stripes and interstripes, blobs and interblobs, and columns and minicolumns. Within each module, adjacent neurons tend to be activated by similar stimuli at similar locations or, for movement-related neurons, to control similar behaviors. Between modules, activity patterns change abruptly. These findings suggest that cortical modules are generated by Hebbian plasticity, which

strengthens connections between neurons that fire simultaneously or nearly simultaneously. Although this form of plasticity is most often invoked as a mechanism for generating topographic maps within the brain, it can also explain the formation of abrupt boundaries, because such boundaries can maximize the overall probability that adjacent neurons fire concordantly. As Kaas suggests, the mechanisms for topographic map and module formation seem to exist throughout mammalian neocortex but also in some other brain regions, such as the frog's optic tectum.

Suzanaerculano-Houzel (28) steps back from the organizational details of mammalian brains and focuses, instead, on the number of neurons and nonneurons (primarily glia) found in the major brain regions of various mammals. Using the isotropic fractionator method, which involves homogenizing brain regions and counting stained cell nuclei in samples from the resulting homogenate, she discovered that neuron numbers scale differently (against brain region mass) in primates and rodents. This finding may explain why primates tend to be more intelligent than other mammals, even when brain mass is held constant: as brain size increases, primates have more neurons per gram of brain tissue than other mammals. Accordingly, Herculano-Houzel argues that absolute neuron number is a better predictor of "intelligence" than absolute brain size. She also points out that human brains contain almost exactly the number of neurons that one would predict, given the primate scaling rules. This conclusion would have pleased T. H. Huxley, if not Darwin himself. Moving beyond these findings, Herculano-Houzel proposes interesting ideas on the evolution of brain energy costs and their relationship to feeding behavior.

From Neural Circuit Evolution to Adaptive Behavior

The five papers that follow aim to link evolutionary changes in neural circuits to the evolution of behavior. James Newcomb et al. (29) describe the neural circuits underlying swimming behavior in various Nudipleura (sea slugs). As it turns out, some nudipleuran species have evolved the ability to swim by undulating their bodies either from side to side or dorsoventrally. Importantly, these different types of swimming evolved independently in several different lineages, allowing for interesting comparisons of their underlying circuitry. Specifically, Newcomb et al. report that nonhomologous swimming behaviors can be mediated by neural circuits that include homologous (as well as nonhomologous) neurons and that clearly homologous swimming in closely related species may involve nonhomolo-

gous neurons. These findings show that, even for homologous behaviors, it is difficult to predict how conserved the underlying circuits are. An important implication of this finding is that one cannot homologize behaviors merely on the basis of how similar their underlying circuits are. This conclusion extends a theme first mentioned in the paper by Northcutt (22): homology at one level of biological organization need not imply homology at other hierarchical levels.

Andrew Bass and Boris Chagnaud (30) review the literature showing that the premotor neurons controlling sound production tend to be derived from caudal rhombomere 8 in the hindbrain of many different vertebrates, including fishes and amphibians. Something about these neurons makes them especially well suited for complex, often rhythmic, pattern generation and for the coordination of diverse muscles, including the muscles related to breathing. Bass and Chagnaud further point out that in toadfishes the hindbrain vocal motor neurons lie adjacent to motor neurons innervating the pectoral fins. This finding suggests that the neural circuitry for sound production shares a long evolutionary (and developmental) history with the circuits controlling the pectoral fins and, in tetrapods, the forelimbs. This hypothesis may seem far-fetched at first; however, pectoral fins are used for sound production in a number of fishes, and forelimbs are clearly used for gestural communication in humans. If correct, the hypothesis implies a deep homology between behaviors that seem quite disparate but involve homologous neural circuits and, presumably, homologous developmental genes.

James Goodson et al. (31) examine variation in neuropeptide expression across multiple brain regions involved in avian social behavior. More specifically, the paper focuses on differences in peptide expression among four emberizid songbird species, examining their correlation with seasonal changes in territoriality and/or flocking behavior. The analysis gets complicated, because variation in the degree of territoriality may be caused by reduced aggression or increased gregariousness (i.e., flocking), which likely involve different neural mechanisms. However, clever species selection allows the authors to identify one set of differences in neuropeptide expression that is most likely linked to differences in aggression and another set that correlates with differences in flocking behavior. As the authors admit, the conclusions are based on just a few species and, therefore, tentative. However, the study undeniably reveals an unexpectedly large degree of variation in peptide levels both across

species and within species (i.e., seasonal variation). This variation is probably a driving force behind the variation in behavior, although it may also be a consequence. Experimental manipulations are needed to discriminate between these two hypotheses.

Lucia Jacobs (32) develops ideas about the role of the hippocampus in navigation. She suggests that olfaction played a crucial early role in the evolution of spatial orientation, providing information about spatial gradients (in odor plumes) as well as local cue constellations (locale-specific odorant mixtures). The hippocampus became specialized to process and integrate these two kinds of information. Subsequently, these functions were extended to other sensory modalities. An interesting corollary of this hypothesis is that the size of the olfactory system should correlate more tightly with an organism's ability to navigate by olfactory cues than with its capacity for odor discrimination. The hypothesis might also explain why olfactory brain regions scale less tightly than other regions with overall brain size. Perhaps the evolutionary shift to multimodal navigation allowed the olfactory system to be reduced. Jacobs predicts that the olfactory system should be larger in species that must predict when and where their food will be available than in species that feed opportunistically.

Kenneth Catania (33) reports on two natural but highly unusual feeding behaviors. First, Catania reviews the incredibly rapid and efficient hunting behavior of star-nosed moles. Using optimal foraging theory, he shows that these small predators are specialized for rapidly finding and eating small aquatic invertebrates. Their star-shaped "nose" evolved to help them in this task, as did a series of related specializations in the brain, including an expanded somatosensory cortex. Catania then turns to an aquatic snake that has evolved a fascinating trick for catching fish. It uses a tiny muscular contraction of its body to trigger a nearby fish's escape response in such a way that the hapless fish tends to swim directly into the snake's wide open fangs. Even more remarkable, the snakes can anticipate the trajectory of the escape response, intercepting a fish before it gets away. Because this predictive ability is found even in naive snakes that have never caught (or missed catching) a fish, it seems to be innate (i.e., unlearned). Why did the fish retain their stereotyped escape response, given that the snakes can exploit it? The answer may be that snakes are relatively rare, and the escape response serves the fish well when dealing with most other threats.

Phylogeny of Human Brains and Human Minds

The papers in this section address the question of human uniqueness in brain organization and behavior. Todd Preuss (34) focuses on molecular genetic differences between human brains and the brains of our closest relatives. Particular emphasis is given to the role of *foxP2*, which has, at times, been called the human language gene. Not surprisingly, the true story of *foxP2* is more complex, because as Preuss puts it, “we are trying to relate a multifunctional gene to a complex, high-level phenotype.” To deal with this complexity, Preuss suggests that we need a better understanding not of single gene variation, but of variation in many genes and, particularly, brain development. Preuss also notes that human brains mature more slowly than the brains of other species, which would explain why brain metabolic activity is surprisingly high and structural plasticity unusually protracted in humans. Particularly interesting is the observation that some patterns of gene expression in the prefrontal cortex of humans are seen only during development in other species. The mechanisms underlying this heterochrony as well as their functional sequelae remain unclear. However, childhood is well-known to be more protracted in humans than in other apes.

Lizabeth Romanski (35) reviews the anatomical and physiological organization of the ventrolateral prefrontal cortex (vlPFC) of macaque monkeys. This cortical region is of special interest, because its homolog in humans includes several language-related areas (e.g., Broca’s area). In a key experiment, Romanski and her colleagues took movies of vocalizing monkeys, separated them into audio and visual streams, and showed them to other monkeys with recording electrodes in their vlPFC. This experiment revealed that the majority of vlPFC neurons integrate auditory and visual information in a nonlinear manner. This finding is important, because human speech perception also involves a considerable amount of audiovisual integration, as demonstrated by the McGurk effect (36). Of course, audiovisual integration of vocalization-related stimuli is not identical to speech perception, which requires the integration of sounds and visual information with meanings. The latter type of integration still eludes the understanding of neurobiologists and is extremely difficult to study in monkeys. Nonetheless, the audiovisual integration that Romanski describes in monkeys is likely to have played a major role in the evolution of human language.

Jessica Cantlon (37) compares the mathematical abilities of nonhuman pri-

mates and humans, especially human children. Although we often think that mathematics requires symbols (e.g., numbers and operators), simple math can be performed without symbols. For example, one can compare two images and estimate, even without counting, which image contains more items of a particular sort. This kind of analog numerical estimation can also be performed by human infants and nonhuman primates. Cantlon further reports that the analog math task activates homologous brain areas in the parietal cortex of both humans and monkeys. Collectively, the data strongly suggest that analog math abilities evolved long before the origin of *Homo sapiens*. This finding is fascinating, but how did symbolic math evolve? Was it built on top of the more ancient analog skill, using the ancient circuitry with only minor modifications? Or did symbolic math evolve out of symbolic communication (i.e., language)? At this point, the answer is unknown.

Clark Barrett (38) dispels the notion—promulgated by some evolutionary psychologists—that adaptive specializations in the brain must be hard-wired modules. To grasp the argument, consider face-selective neurons in primate brains. Given the importance of conspecific faces in the lives of most primates, the distinct patches of face-selective neurons in monkey and human brains were likely shaped by natural selection. Nonetheless, the development of face-selective neurons probably depends on extensive experience with faces. Indeed, Barrett hypothesizes that selection generated not an innate face-processing module but a set of mechanisms that, given experience with faces, will generate a large number of neurons that selectively encode faces. Given other types of experience, the same mechanisms would (and do) generate patches of neurons selective for other kinds of behaviorally important stimuli. Stated succinctly, Barrett argues that natural selection generates developmental norms of reaction rather than experience-independent specialized modules. This idea extends evo-devo neurobiology into the realm of evolutionary psychology.

A Tangled, Multilayered Web

Reviewing the publications assembled in this supplement, we do not see a tightly woven web. Instead, we see diverse perspectives on a much larger nexus that is as yet largely obscure. This larger web is full of interacting molecules, neurons, brain areas, and entire organisms, all changing through development and over evolutionary time. Neuroscience as a field is already complex, but when one adds the evolutionary dimension, the complexity becomes

truly awesome and certainly beyond what one can expect to capture in just a few colloquium papers. Nonetheless, some recurring themes emerge.

One idea running through several contributions is that evolution and development are linked. Historically, evolutionary neurobiologists visualized evolutionary changes as transformations between adult forms. This thinking changed with the emergence of evo-devo biology, which was slow to infiltrate neurobiology but is now ascendant (39–42). According to this view, evolutionary changes must involve changes in development, which can be inferred by comparing developmental mechanisms and trajectories between species. Such comparative developmental studies can reveal the mechanistic basis of evolutionary change and, thus, complement studies that address the ecological and behavioral contexts in which those changes might have been adaptive.

A second theme woven into several of the colloquium papers is that homologies at one level of biological organization may or may not be linked to homologies at higher or lower levels (43). For example, similarities in the expression patterns of homologous genes are sometimes used to argue for the homology of the structures in which those genes are expressed, but the genes might well have existed before the higher level structures came on the scene. As long as genes can change their functions over evolutionary time, this possibility is not easily dismissed. Even complex networks of interacting genes are, as Jarvis et al. (23) argue, capable of becoming involved in the assembly of novel structures. If similar changes in function occur independently in multiple lineages, then the structures would be nonhomologous, even though the underlying genes are homologous. In such cases, one might say that the structures are “deeply homologous” but “superficially nonhomologous”, although this terminology is likely to engender confusion.

Analogous challenges arise in comparative neuroethological studies. One can certainly homologize behaviors, be they swimming in snails or math skills in primates, but those behavioral homologies offer only loose predictions about the homology or nonhomology of the underlying neuronal circuits. If neurons can change their behavioral functions over evolutionary time, then homologous behaviors may involve nonhomologous neurons, and nonhomologous behaviors can involve at least a few homologous neurons. This point has been made before by various authors (44), but it continues to befuddle the unsuspecting mind. As mentioned earlier, the task of understanding how the tangled bank of molecules, cells, structures,

organisms, and behaviors has managed to transform itself in evolutionary time has only just begun. Still, as this PNAS supplement aims to show, some progress has been made, especially if we compare our

current state of knowledge with the knowledge in Darwin's time.

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series (J.C.A. and F.J.A.) are the academic grandson and son, respectively, of Theodosius Dobzhansky, to whose fond memory this series is dedicated. May Dobzhansky's words and insights continue to inspire rational scientific inquiry into nature's marvelous operations.

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