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LESSONS FROM EVOLUTION

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When invited to contribute to this book, *The Future of the Brain: Essays by the World's Leading Neuroscientists*, I agreed for two reasons. The first and most obvious is that I study the brain. However, as an evolutionary neurobiologist I am more interested in its past than in its future. The second reason is based on pure vanity; who could resist agreeing to be included among the "world's leading neuroscientists"? In this essay I reflect on a few important things I've come to appreciate about brain function and evolution, where I think we should direct our future energies in trying to understand the brain, and end with a brief assessment of our current ability to predict future brain evolution.

One of the first and most important lessons I have learned as a neuroscientist is that in order to understand how complex brains evolve and work, it is not enough to study only complexly organized brains. As a young graduate student, I was interested in why humans behave the way that they do, how the brain generates this behavior, and how both the brain and behavior evolve. Although much of my graduate work was on the brains of nonhuman primates, I ultimately concluded that to truly understand how complex brains evolved, looking at our close relatives like monkeys would never be enough. Although monkey brains are extremely complex, there are important insights to be gleaned from a wide variety of species. For example, we know from comparative studies in mammals that the neocortex, the part of the brain involved in perception, cognition, and volitional motor control, varies dramatically in size and the number of interconnected cortical fields (functional subdivisions of the neocortex) in different species. Comparative studies indicate that a large neocortex with multiple parts evolved in primates, including humans, but also evolved independently in other lineages such as cetaceans (whales and dolphin). In order to appreciate how these types of complex brains evolved, I felt it was critical to appreciate how the neocortex of early mammals was organized and then determine the types of alterations that were made to the brains of their descendants. Thus I ventured to Australia where I could study mammals whose ancestors branched off early in evolution (monotremes and marsupials) in the hope that they would have retained some primitive features of neocortical organization inherited from our early ancestors over two hundred million years ago. While in Australia I found that monotremes and marsupials have the same basic plan of neocortical organization that all species possess, and that this plan has been elaborated in different lineages. Thus every living mammal, including humans, has aspects of neocortical organization and connectivity that were inherited over two hundred million years ago from the common ancestor of all mammals.

The second important lesson I learned is that unusual mammals can tell us a lot about the rules of brain construction and brain/body relationships. Comparative studies on animals that possess extreme specializations like the duck-billed platypus, star-nosed mole, or echolocating bat provide important insights about the human brain. For example, the duck-billed platypus has a highly specialized bill with electrosensory receptors and uses this specialized body part for navigating, mating, and prey capture in the water. This specialized body part is associated with a number of brain features, such as cortical magnification or the amount of cortex devoted to processing inputs from a specific body part. The platypus is unique in the extraordinary magnification of its bill; about 90 percent of its somatosensory cortex is devoted to the bill representation. These body specializations in mammals are also associated with the types of stimuli that neurons respond to and alterations in the connections of the brain. Studies on animals that are highly specialized also inform us about the importance of use of this specialized body morphology in constructing the brain during development and the dynamics in shaping the neocortex as an organism matures to adulthood. If we consider human specializations in this same light, we would conclude that specializations of the vocal tract and oral structures associated with speech production have a large portion of the neocortex devoted to processing these inputs, and these areas have altered connections associated with these specializations—and, they do. As Ted Bullock elegantly articulated in his *Science* essay, "Comparative Neuroscience Holds Promise for Quiet Revolutions," comparative studies are important in revealing the *roots* or evolutionary history of brain organization, the *rules* of construction of brains and the constraints under which the nervous system develops and evolves, and the *relevance* or general principles of brain organization. Thus while we may be interested in how complex brains like those of humans arose, we must admit that most insights about general rules of construction and general principles of neocortical function come from the brains of other mammals.

The third important lesson is that the brain does not develop or function in a vacuum. For years I used comparative analysis in a variety of mammals to determine how the brain, particularly the neocortex, was modified throughout the course of evolution, and the factors that contribute to aspects of the cortical phenotype such as organization and connectivity. I was extremely "braincentric" when considering these issues, and this was due, in part, to my early training. Although I worked on multiple species as a graduate student, my experiments were restricted to listening to and looking at the brain using electrophysiological recording techniques and neuroanatomical techniques, respectively. My point is that I never seriously considered other parts of an animal except its brain. Perhaps one of the biggest revelations in my career came when I began a postdoc in Australia and had to *catch* the animals I worked on—a moment I still remember with clarity: late at night rowing a boat in murky waters, hoisting gill nets and hoping like hell there would be a platypus caught in the net. I vividly recall marveling over the texture and composition of its bill, its tiny eyes, its webbed paws and unbelievably thick, water-resistant fur, and wondering what it would be like to be a platypus. When I discovered the extraordinary amount the neocortex devoted to processing inputs from the bill, I finally realized my curiosity never could be satisfied. Although my brain shares a number of features of organization with the platypus, I don't have a hydrodynamically constructed body like a platypus, nor massive inputs from mechanosensory and electrosensory receptors on a bill pouring into my brain. Brains do not operate in isolation but are embedded in a body, often containing specialized sensory receptor arrays, and the whole animal develops and evolves in a context of both animate and inanimate objects, conspecifics (same species), and heterospecifics (other species), all of which are constrained by the laws that govern matter and energy on our planet.

The fourth important lesson learned was that genes are not everything. It is becoming more and more apparent that epigenetic mechanisms—which alter transcription or expression of genes—are critical for constructing a brain that is highly adapted to the context in which it develops and in which the animal will ultimately live.

Conrad Waddington first used the term *epigenetics* in the middle of the last century in an effort to explain cellular differentiation during development. If there is a one-to-one correspondence between DNA and the phenotype, then every somatic cell in the body (which contains exactly the same genotype) would be identical. Instead, the phenotypes of cells vary from brain cells (neurons) to liver cells. Because of this, Waddington proposed that the mechanisms through which a genotype produces a phenotype should be termed *epigenetics*.

Considering that cellular phenotypes undergo dramatic plasticity during development while the genotype of these cells remains stable implicit in Waddington's definition is the notion that a phenotype can be altered without changes to the genotype. Thus during the course of development, epigenetic mechanisms (such as DNA methylation, a biochemical process that reduces gene expression in specific portions of the brain and body) allow cells with the same DNA to differentiate and divide, passing on those alterations in gene function, not explained by alterations in DNA sequence, to daughter cells. If we expand this concept to take into account the fact that an organism does not remain static throughout the lifespan, but rather it dynamically responds to social and environmental contexts, then epigenetic mechanisms might also mediate the adaptability of brain and behavior to the environment. Recent work from the laboratories of Michael Meaney and Frances Champagne indicates that variation in early development induces epigenetic variation (in DNA methylation for example) and may serve as a mechanism for developmental plasticity. For example, alterations in nutrition, stress, and maternal care early in life can trigger these epigenetic mechanisms and generate anatomical and functional changes to the brain and body, which alters behavior of the offspring. These alterations in behavior can be sustained across generations via epigenetic effects on portions of the neuroendocrine system, or in some instances persist through epigenetic effects on the germ line.

The dramatic role that epigenetic mechanisms play in shaping brain and behavior is well exemplified in humans. Anatomical alterations to the hand necessary for complex bimanual dexterity; to the supralaryngeal tract necessary for speech production; and to the inner ear, which amplifies frequencies associated with human speech, were present well before these behaviors that we attribute to modern humans were expressed within the population. Thus the anatomical underpinnings for complex human behaviors were present in our very early ancestors and those of our Neanderthal cousins, but complex behaviors like language and sophisticated and precise tool use (generated by the neocortex) were shaped by the social and cultural context in which individuals developed, rather than traditional evolutionary mechanisms. We know from our own work and from that in other laboratories that context, which can be considered as complex and dynamic patterns of incoming sensory information available to developing brains, can alter neocortical connectivity, functional organization, and the resultant behavior of an individual. Remarkably, it is possible to dramatically alter "normal" brain connectivity and function by altering the patterns of stimuli experienced during development and over a lifetime.

This leads to my fifth revelation: there is no single or optimal way to build some feature of brain organization. For years I searched for "the way" in which some aspect of the cortical phenotype could be altered during the course of evolution. For example, what is the way in which the size of cortical fields is altered? What is the way in which cortical connections change? What is the way in which cortical fields are added? Studies of molecular development that examine genes intrinsic to the developing neocortex have demonstrated how these genes (and genetic cascades) can alter cortical field size, location, and connectivity. Interestingly, these same features of organization can be altered by the sensory driven activity that the developing organism is exposed to. Because cortical field size and connectivity can be changed through different mechanisms, this implies that in a given lineage, some aspect of brain organization owes its particular phenotype to genes, activity-dependent mechanisms, or some combination of both. However, a similar phenotype in a different mammal may have arisen by a very different combination of these factors.

From a personal rather than scientific standpoint, the final important thing I've learned is don't be taken in by the boondoggle, don't get caught up in technology, and be very suspicious of "initiatives." Science should be driven by questions that are generated by inquiry and in-depth analysis rather than top-down initiatives that dictate scientific directions. I have also learned to be suspicious of labels declaring this the "decade of" anything: The brain, The mind, Consciousness. There should be no time limit on discovery. Does anyone really believe we will solve these complex, nonlinear phenomena in ten years or even one hundred? Tightly bound temporal mandates can undermine the important, incremental, and seemingly small discoveries scientists make every day doing critical, basic, nonmandated research. These basic scientific discoveries have always been the foundation for clinical translation. By all means funding big questions and developing innovative techniques is worthwhile, but scientists and the science should dictate the process. There are numerous examples where individuals, rather than top-down initiatives, worked to progressively cure or prevent diseases or uncover important and fundamental principles of biology. Some of these include Jonas Salk's vaccine for poliomyelitis; Santiago Ramón y Cajal's discoveries on the anatomical structures of neurons and his articulation of the neuron doctrine; and of course Charles Darwin's detailed observations that led to the theory of evolution through natural selection, which is now the cornerstone of all of biology.

Of course most of these lessons learned during my career have been well documented by erudite neuroscientists well before me. However, this personal synthesis has shaped my own science and the evolution of my thoughts, and it certainly plays a heavy hand in where I believe we should direct our future energies as neuroscientists. First, I think that revealing the relationships between multiple levels of organization, from genes to neurons to cortical maps to behavior, is critical. This will require those of us working in science to step out of our individual scientific comfort zones and to consider levels of organization larger and smaller than the one at which we personally work. Our quest for understanding species differences must move well beyond comparative genomics and approaches that seek simple genetic explanations for complex phenomena such as language, autism, or schizophrenia. In our enthusiasm for genetics, we often seem to have sidestepped systems neuroscience, cognitive neuroscience, social science, and whole animal physiology, prematurely narrowing our search to uncover unrealistically direct gene-to-complex-behavior relationships. As noted above, context is extremely important, and in terms of human brain organization and function, culture appears to have played a pivotal role in shaping the human brain and modern human behavior.

Given the enormous role of social and cultural context in human brain organization and function, to predict the future evolution of the brain—where our own brains might be a hundred or thousand or a million years from now—would require us to predict the direction of social, economic, and technological changes to our current culture. We also need to consider the physical changes in the environment like global temperature, the types of food we eat, the chemical treatment of our water, alterations in our form of locomotion, and our movement away from traditional tool use to automation and skills that require more unique movements of our digits, all of which may shape our future body morphology, physiology and metabolism. In short, you can't predict future brain organization in isolation, but must consider the multilayered context in which the brain develops.

Having said this, I contend that understanding the history of brain evolution does provide powerful insight into understanding the types of alterations that can be made to brains in the future. Evolution of the neocortex can be considered, to some extent, as an ever-diminishing set of options. Genetic contingencies and pleiotropy (a single gene has multiple, seemingly unrelated effects) place formidable constraints on brain development as do the laws of physics, and comparative studies demonstrate that the types of changes that have been made to the neocortex through the course of evolution are limited. While no one can predict the exact phenotype that the next million years of human evolution will produce, one can infer the types of alterations that can be made to the human brain, as well as alterations that are improbable. One can also predict with a high degree of confidence that concrete anatomical and physiological alterations that generate complex behavior will be due to alterations in genes that covary with some aspects of the body, brain, and behavior, but these features will always be couched with cultural evolution and will emerge and often persist through epigenetic mechanisms.

Finally, for all I have learned, probably the most important revelation in my own journey has been the continuing and exhilarating process of realizing how little I really know, and how much there is still to explore.