VII.1

Genes, Brains, and Behavior
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OUTLINE

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4. Analyzing behavior: Natural variation versus mutations
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Behavior is defined as the directed action of an animal in response to a stimulus. In multicellular animals, behavior is the product of the nervous system. Behavioral phenotypes are often conserved across distant taxa and are heritable. Yet, the role of genetics and evolution in determining behavior has been controversial for much of the first half of the twentieth century, often paraphrased as the "nature versus nurture" debate. While heredity clearly plays a role in behavior, linking "behavioral" genes to behaviors has not been easy. Two primary approaches have been used over the years to identify causal loci: studies of natural variations in wild-type populations and mutagenesis-dependent forward genetic screens. Both approaches have strengths and limitations; while mutation analysis has been immensely successful in identifying many causal genes, it is blind to the evolutionary and population levels forces that shaped behaviors. In contrast, studies of natural behavioral variations have often failed to identify causal relationships between specific genetic polymorphisms and the studied phenotype. However, the methodological dichotomy is fast disappearing owing to the exponential pace of technical and theoretical advances in molecular biology, resulting in an improved understanding of how the interactions among genes, brains, and the environment lead to specific behaviors.

GLOSSARY

Central Dogma. The concept, proposed by Francis Crick in 1970, that all cellular proteins are produced via a linear and nonreversible process in which "gene"-specific information encoded in DNA is transcribed into a messenger RNA (mRNA), which subsequently gets translated into a protein.

Circadian Rhythms. Internally driven, circa 24-hour cycle in biological systems.

Epigenetics. In general, an often transient heritable change in gene expression caused by factors other than changes in the underlying DNA sequence (mutation). In this chapter this term is used to describe the role of chemical modification of DNA and histone proteins by methylation and/or acetylation as a mechanism for regulating gene function in a tissue-specific manner. Under certain circumstances, such modifications can be heritable without any changes to the primary DNA sequence and hence constitute a mechanism for non-genomic inheritance of quantitative traits. It is important to note that epigenetics means different things to different people in different biological fields.

Ethology. The study of behavior of animals in their natural environments. Konrad Lorenz, Karl von Frisch, and Nikolaas Tinbergen won the Nobel Prize for Medicine in 1973 based on their work in this field.

Eugenics. A popular social movement in the early twentieth century that advocated the use of selective breeding for the improvement of hereditary traits of a specific race, often applied in the context of humans.

Experimental Psychology. The study of animal behavior under controlled laboratory conditions. The psychologists Ivan Pavlov and B. F. Skinner were seminal in developing animal models for cognition, although neither studied genetics.

Forward Genetics. An approach for identifying genes underlying a specific phenotype without any a priori assumptions in regard to their identity or biochemical functions.

Genomics. Studies of whole-genome architecture, including DNA sequences, analyses of whole-genome transcriptional regulation, and the role of genome evolution in biological processes such as speciation or heritable diseases.

Geotaxis. The behavioral response of organisms to the vector of gravity, which can have a negative or positive value—that is, move up (negative) or down (positive).

Phototaxis. The behavioral response of organisms to light, which can have a negative or positive value—that is, move away from (negative) or toward (positive).

Pleiotropy. The effects of the function of a single gene on multiple, independent phenotypes.

Quantitative Trait Loci (QTL). Sequence(s) of underlying DNA associated with complex, non-Mendelian, polygenic traits. Each contributing QTL is independently variable in the studied population and hence is responsible for a defined proportion of the overall observed phenotypic variability.

Reverse Genetics. A "candidate gene approach," which implicates previously characterized genes with a novel phenotype.

Systems Biology. An emerging biological framework that promotes a holistic approach to understanding complex biological systems, based on the idea that complex biological systems have irreducible emergent properties that cannot be understood by studies of simpler individual elements.

Systems Genetics. Genetic studies using systems biology, especially in the context of non-Mendelian complex phenotypes, based on the principle that understanding complex phenotypes such as behavior depends on understanding interrelationships among genotypes and phenotypes at the organismal level.

1. GENES AND BEHAVIOR

Behavior is one of the characteristic traits of animals and can be defined as a reaction in response to specific changes in an individual's environment. Despite this ubiquity, finding a simple and common description of behavior is elusive, perhaps in part because the term *behavior* covers so many different actions. This staggering behavioral diversity across the animal kingdom and the inherent phenotypic range associated with behavior have often led to a common belief that behaviors are unique phenotypes that cannot be explained within the general biological framework. Yet, many behaviors are stereotypic and seem to be driven by common molecular pathways across

diverse and distant animal taxa. Examples of commonality among many animals include aggression over territories (see chapter VII.5) and mates (see chapter VII.6), foraging for food when hungry, circadian rhythms, and the avoidance of harmful chemicals or extreme temperatures. Even the most plastic of traits—learning and memory and cognition (see chapter VII.14)—have genetic homology across organisms.

The conservation of specific behaviors across generations of the same species—independent of cultural and learned phenotypic transmissions—and its evolution over time can mean only one thing: behavior is the product of information encoded in DNA. Yet, the acceptance of behaviors as genetically inherited phenotypes shaped by natural selection has long been controversial. This chapter explains and discusses some of the confusions associated with behavioral genetics. It also examines the role behavior has played in animal evolution, and the impact of evolutionary thinking on studies of animal behavior.

Behavioral genetics emerged during the first half of the twentieth century as a multidisciplinary field that built on foundations drawn from important advances in several areas of the modern biological sciences, including statistics, ethology, and experimental psychology. Study in these fields led to the realization that behaviors are often conserved across distant species, that general behavioral principles can be learned by observing animals, and that behavioral traits can be shaped by both natural and artificial selection. The second important contribution to behavioral genetics thus came from the work of Theodosius Dobzhansky and his colleagues, and led to the modern synthesis that linked evolutionary theory with genetics. This synthetic framework also included the work by J. B. Haldane, Sewall Wright, and R. A. Fisher, which laid the foundation for the development of population genetics, a discipline that uses quantitative approaches and empirical studies to understand the role of allelic frequencies in populations and the effect of these genetic variations on observed phenotypic diversities.

The third important contribution to behavioral genetics was the emergence of molecular genetics in the second half of the twentieth century, which was fueled by the discoveries of the double helix model for the DNA structure and the development of the *central dogma* in molecular biology (DNA to RNA to protein). These discoveries, in combination with rapid technological advancements, resulted in the ability of geneticists and evolutionary biologists to obtain DNA sequences of specific genes from individuals, revolutionizing the fields of evolution and genetics. For the first time, biologists were able to associate phenotypic variations with physical DNA polymorphisms. These advancements enabled

biologists to interpret function and evolution of morphological, physiological, and behavioral traits by studying the DNA sequence and the genetic architectures at the complete genome level.

The fourth important scientific development was the emergence of modern neuroscience. This field served as the foundation for understanding how multicellular animals can integrate and process stimuli, and translate them into an action, a "behavior." Better understanding of the biology of neurons enabled the placement of behavioral genetic findings in the context of the primary organ that drives behavior, the nervous system.

The rest of this chapter presents the theories and empirical data that support the role of genes and evolution in behavior and explains the synergistic role behavioral genetics plays in modern evolutionary thought.

2. "NATURE VERSUS NURTURE"

First coined by Galton in his book *English Men of Science: Their Nature and Their Nurture* (1874)—and despite his perspective that both nature and nurture are important in the development of behavior—the expression "nature versus nurture" became synonymous with the controversies associated with the field of behavioral genetics. The introduction of heredity, and later genetics, to the fields of animal behavior and evolution met with much resistance, likely stemming from earlier views by philosophers such as John Locke, who suggested that all people are born as a *tabula rasa*, or blank slate. The *tabula rasa postulate* asserted that all humans are born equal in terms of their cognitive and behavioral capacities, and it is only their experiences that shape who they become. In contrast, many of the early geneticists in the United States and Europe promoted the hereditarian (nature) view of behavior, which was dominant for most of the first half of the twentieth century. This interpretation resulted in the application of Mendelian genetics, sometimes in the most absurd ways, to many human and animal behavioral traits. These deterministic views changed rapidly during the 1950s as *behaviorism* became a popular philosophical view of human and animal behavior. Guided by the writings of leading experimental psychologists such as J. B. Watson and B. F. Skinner, behaviorists dismissed altogether the role of heredity in determining behavior and advocated that only life experiences matter in shaping an individual's behavior (nurture).

Most modern-day researchers who study human or animal behavior would agree that the nature versus nurture dichotomy is, in fact, oversimplified and archaic, although it is still prevalent in the scientific literature. No organism develops without genes (nature), and no organism develops in the absence of an environment (nurture). Furthermore, as the field of molecular genetics matured, it became clear that many behavioral phenotypes are complex and do not follow simple single-gene Mendelian rules. While the mounting evidence supports the hypothesis that heredity and genetics have an influence on behaviors, most behaviors show a continuous distribution of values (i.e., are *quantitative traits*) rather than a collection of discrete phenotypes. Hence, a refined view of the nature versus nurture debate is that information stored in the DNA determines behavioral phenotypic boundaries rather than specific phenotypic values. This model suggests that a specific behavioral phenotype can be stretched in multiple directions dependent on the strength of the various internal and external stimuli relevant to the phenotype in a species-specific context. Moreover, as is discussed toward the end of this chapter, certain plastic phenotypic alternatives can become fixed across generations via nongenomic, epigenetic mechanisms.

3. WHAT IS A "BEHAVIORAL GENE"?

Despite the tendency of people (and newspapers) to speak of "genes for behavior," specific genes might not necessarily encode directly for a specific behavior but, rather, are shaped by evolution to set physiological and physical constraints on the expression of behavioral phenotypes. Unfortunately, and perhaps confusingly, geneticists frequently assign specific "functions" for their genes, in ways that simplify their long-term research goals but that lead to the perception that specific genes cause specific behaviors. For example, the scientific literature contains descriptions of genes classified as a "developmental gene" or a "cancer gene." The field of behavioral genetics, which is strongly influenced by developmental biology, followed the categorization of genes with the identification of various "behavioral" genes. Examples included "learning and memory genes," "social genes," and "sex genes." However, genes do not encode for phenotypes such as cancer, development, or specific behaviors. Rather, genes encode for RNAs and proteins. It is the biochemical function of these macromolecules, and the cellular processes they fuel, that drive processes such as the occurrence of cancer, normal development, or the expression of a specific behavioral phenotype (Robinson et al. 2008).

Modern neuroscience teaches that in all multicellular animals, a behavior is the product of the nervous system, a complex and highly specialized organ made of many individual neurons organized in stereotypical neuronal circuits. Therefore, "behavioral" genes and genetic variations are likely to affect behaviors indirectly by determining the development of specific neuronal circuits, their interactions with other organs and cell types, and

the capacity of neuronal circuits to respond physiologically to changes in the internal and external environments of individuals. Behavior is typically flexible, quantitative in expression, and difficult to study in genetic terms because of these multiple inputs. Any and all of these levels can be genetically influenced. Nevertheless, none of the levels is purely environmental.

4. ANALYZING BEHAVIOR: NATURAL VARIATIONS VERSUS MUTATIONS

As mentioned in the previous sections, studies of behavior and cognition played a major role in the early days of genetics. In contrast with the scientific fallacies that were associated with eugenics, many positive influences on modern biology were associated with the emergence of the field of genetics, in the work of Arthur Darbishire, Robert Yerkes, E. C. Tolman, and others. These pioneers took advantage of various animal models to investigate the role of heredity in specific behaviors. Their studies were not confined to natural behaviors but also tried to understand the genetics and inheritance of "abnormal" behaviors and the insights they might bring to elucidating how nervous systems drive specific behaviors. Illustrative examples are the studies on heredity in the "Japanese waltzing mouse," a mouse breed that exhibits a tendency to run in circles, and selection studies by E. C. Tolman used to generate rats that were either "dulls" or "brights" in learning how to navigate a maze for a food reward. The latter studies indicated a strong genetic basis for cognitive abilities in rats.

The negative connotations associated with the eugenics movement, and the related atrocities of World War II, led to the disenchantment of many human and vertebrate behaviorists with genetics. But other model systems emerged to support the role of genetics in behavior. Some of the strongest support for the function of heredity in behavior came from studies of the genetic workhorse, the fruit fly *Drosophila melanogaster*, driven by the seminal works of T. H. Morgan and his students. The fly turned out to be an excellent genetic model owing to its small genome, short generation time, adaptability to laboratory conditions, and rapid response to selection and mutagenesis. One of the first to use the fly purely as a model for behavioral studies was Jerry Hirsch, who trained with Tolman, and was influenced by Dobzhansky's views on population genetics. Hirsch (1963) used flies and artificial selection to decipher the "genetic architecture" underlying natural behavioral variation. Hirsch asserted that the only way to understand how behaviors evolve, and what role genetic variation plays in specific behavioral phenotypes, is to use the tools of population and quantitative genetics to quantify the relative contributions of specific *quantitative trait loci* (QTLs) to the overall behavioral variations within a population. An underlying assumption in his studies was that multiple independent genes contribute to behavioral phenotypes and that allelic variations in each locus contribute a defined fraction of the overall behavioral variations in a population. One of his studies that best illustrated this approach was a long-term selection study of flies that showed a strong positive or negative response to gravity (geotaxis). Wild-type flies tend to be somewhat negatively geotactic (run "up" when disturbed). Hirsch selected for genetically homogenous *Drosophila* strains that showed either extreme positive or negative geotaxis behaviors. He then used chromosomal mapping techniques to estimate the quantitative contribution of each of the fly's three main chromosomes to the genetic differences in behavior between the two extremes. His conclusions were that even for a relatively simple behavior such as geotaxis, many genes contribute to the genetic divergence between the two strains and the responsible genes are likely distributed across all three chromosomes. Hence, his selection led to the allelic stabilization of multiple independent genes, rather than changes in a single major gene. His studies fell short of identifying the specific loci responsible for the behavioral differences between the lines.

While Hirsch's approach to behavioral genetics was strongly influenced by experimental psychology and quantitative genetics, other approaches to studying the genetics of behavior emerged in the early 1960s. The most influential work came from the laboratory of Seymour Benzer, who was strongly influenced by the emergence of the use of mutagenesis to study molecular genetics and the transformative effect it had on the fields of embryology and developmental biology; he saw an overlap with behavior. This profound insight was best captured in his first publication on studies of behavioral genetics in *Drosophila*:

> Complex as it is, much of the vast network of cellular functions has been successfully dissected, on a microscopic scale, by the use of mutants in which one element is altered at a time. A similar approach may be fruitful in tackling the complex structures and events underlying behavior, using behavioral mutations to indicate modifications of the nervous system. (Benzer 1967)

To succeed, Benzer's approach had to rely on the premise that although many genes might contribute to a specific behavioral phenotype, mutations in a single gene could still have measurable effects on the studied

behavior relative to wild-type animals of otherwise identical genetic background. Like Hirsch, Benzer chose to apply his approach first to a relatively simple behavioral phenotype, phototaxis (attraction to light). He devised a clever assay to measure the phototactic response of flies, in which close to 100 percent of wild-type flies showed positive attraction to light. He then used chemical mutagenesis and screened hundreds of animals for any deviations from the expected wild-type behavior. The approach turned out to be immensely successful. Benzer isolated many different phototaxis mutations in individual genes. In contrast with Hirsch's approach, Benzer's studies rapidly identified causal genetic effectors associated with different behavioral and neurophysiological phenotypes such as the molecular identity of the circadian clock, learning and memory, and sexual behaviors (Weiner 1999).

Benzer's successful forward genetics approach, however, comes with a scientific cost. While several animal species are highly amenable to mutagenesis screens, and hence became the darlings of the behavioral genetics community, many others, including people, are not. As a result, much of what we know about the roles of specific genes in neurogenetics and behavior comes from very few model organisms, primarily the fly, mouse, and roundworm. Furthermore, the dominance of mutation analysis studies at the expense of quantitative population genetics led to a major gap in our understanding of behavior in the context of natural selection and evolution.

Many of the early behavioral population geneticists often concluded their studies by saying that the associations between specific genes and behaviors are too complex to allow identification of causal relationships. Yet, in cases where a single major polymorphic gene was involved, it was possible to do so. An example of a success story involves the *foraging* gene. *Drosophila* larvae exhibit a natural polymorphism in foraging behavior; when placed on a yeast lawn, some larvae tend to move rapidly while consuming food ("rovers"), while others seem to slow down significantly ("sitters") (Osborne et al. 1997). Genetic analyses indicated that this behavioral polymorphism is mediated by variations in a single major gene. When the gene was finally cloned, it turned out that it encodes a cGMP-dependent protein kinase (PKG), a protein present in all cells and important for activating or inactivating other proteins by mediating phosphorylation. In the case of foraging, high levels of enzyme activity were associated with "rovers," while lower activity was associated with "sitters." Subsequently, it has been found that the role of PKG in regulating feeding behaviors is highly conserved across different animal species. For example, studies suggested that a homologous PKG gene in honey bees and other social hymenopterans (bees, wasps, and ants) is regulated in association with the division of labor among workers (Ben-Shahar 2002). These studies indicated that changes in the foraging gene activity are associated with feeding behavior plasticity in different species albeit on different timescales: an evolutionary timescale in flies, and a developmental timescale in social insects. The foraging gene story illustrates that complex natural behaviors, undoubtedly influenced by many genes, can still be studied from the standpoint of the contribution of a single gene.

5. GENOMES AND SYSTEMS GENETICS

The early success of Benzer's single-gene-mutations approach to behavioral genetics, and despite a handful of examples such as the *foraging gene* account regarding single genes and their influence on behavior and evolution, suggested to molecular biologists that the approach of Hirsch and some of the other early evolutionary geneticists who studied behavior would disappear from the scientific literature because of the difficulty in identifying the actual molecules, genes, and genetic networks that underlie natural variations in specific behavioral traits. Fortunately, this has not happened, and indeed, the trend is toward studies of more species and more natural variation in behavior. The sequencing of the human genome and the plethora of genome projects that followed led to the reevaluation of studies of natural genetic variations underlying the biology of complex traits, including behavior. This reevaluation was also fueled by the need for a better understanding of the mechanisms underlying complex human behavioral traits, and the rapid transition of evolutionary biology into a molecular biology field.

The exponential growth in biological data acquisition led to the emergence of a "new" biological framework, often termed *systems biology*. The idea behind this approach is that to understand how biological systems work, one has to investigate the emerging properties of the system as a whole rather than looking at its parts individually. *Systems genetics* is a branch of this framework based on the assertion that all organizational levels of biology are interconnected in a complex network that includes both genetic and phenotypic elements, and it is the network that determines the biological characteristics of an individual, or even a group of individuals (Mackay et al. 2009). This approach is in contrast with Mendelian genetics, which looks at each gene as an independent genetic factor.

What is the impact of systems genetics on behavioral genetics? One view argues that there is nothing new in the systems genetics approach, that it is, rather, a rediscovery

of the work of Hirsch and others. Nevertheless, the application of new molecular, genetic, and statistical techniques makes systems genetics an exciting field, with its increasing focus on multiple levels, genes, and natural variation. A great example comes from a study that revisited Hirsch's geotaxis studies. In spite of Hirsch's original assertion that the genetic architecture underlying geotaxis behavior is too complex to allow identification of specific contributing loci, Ralph Greenspan and his colleagues used gene expression microarrays, which can be used to simultaneously examine relative expression levels of thousands of genes from a single source, to identify genes that were differentially expressed in the heads of Hirsch's high and low geotactic fly strains. This effort yielded several candidate "geotaxis genes," which were further confirmed by single gene mutations as playing a major role in the geotaxis response of individual flies. Thus, more than 40 years after Hirsch's publication of his geotaxis studies, modern genetics was finally able to merge the approaches of Hirsch and Benzer to decipher the genetic architecture underlining this ecologically and naturally varying relevant behavior.

The efforts to combine genome-level information with natural genetic variations to identify loci responsible for complex behaviors are ongoing. In spite of early difficulties in pinpointing such traits (as in Hirsch's early geotaxis studies), several recent advances suggest that the identification of loci responsible for quantitative behavioral traits is an attainable goal, especially in genetic model organisms such as the fruit fly and the nematode (roundworm). One of the best examples of the use of recent advances in DNA sequencing for creating modern tools for systems genetics comes from the *Drosophila* Genome Reference Panel (DGRP)—a collection of 192 naturally derived inbred lines with fully sequenced genomes generated by Trudi Mackay and her colleagues (2009). The lines can be screened for any number of complex behavioral traits that can then be mapped to specific variable regions in the fly genome. Furthermore, the DGRP is a community resource, which allows many different research groups to perform behavioral screens using the exact same fly populations. Consequently, phenotypic data generated by the research community could be used to identify genetic variations that affect multiple different behaviors—indicating a pleiotropy between traits—as well as to obtain precise estimates of the contributions of genotype by environmental interactions to specific behaviors. Recent similar approaches taken by C. Bargmann, L. Kruglyak, and colleagues successfully identified several quantitative trait loci associated with complex variable behaviors such as "social feeding" decisions, and the response to specific sensory stimuli in the roundworm. In both cases, at least one major gene was identified as responsible for the quantitative

behavioral differences between different wild-type individuals. While the tools mentioned are currently available for very few genetically tractable model organisms, it is likely that as DNA sequencing techniques become more economical and more readily available, such tools will be increasingly useful in studies of behavioral genetics and the evolution of behavior in other animals as well.

6. THE FUTURE OF BEHAVIORAL GENETICS: THE BEHAVIORAL EPIGENOME

Despite the successes in identifying genes, QTLs, and transcriptional differences associated with various behaviors, the flexibility of behavior remains something of a mystery. Why can it change rapidly in response to changes in the environment? This gene-by-environment interaction and its role in producing variable behavioral phenotypes is still a major unresolved issue. Identifying the interactions among genes, environments, and flexibility fit will have many important implications for basic biology and in clinical studies of human behavior. The problem is simple even if the answers are complex or hidden: how do we reconcile the slow change of genetics (over generations) with the rapid change of behavior (over hours or minutes)?

One fascinating area in which significant progress has been made in this regard is in *behavioral epigenetics*. Studies of epigenetics focus on specific chemical modifications to DNA and nucleosomes during development. These modifications affect gene transcription in a tissue-specific manner. Recently, principles of epigenetics have been applied to explain how some specific life experiences might lead to differential behavioral outcomes in a group of animals with otherwise identical sequences of DNA. It is beyond the scope of this chapter to describe in detail the current state of knowledge in the field of epigenetics given that it is relatively new and changing rapidly. Instead, we will focus on one well-established example of the important role epigenetics is playing in the heredity of specific human and animal behaviors.

The idea that environmental changes during development could affect the behavior of adult animals is as old as the nature versus nurture debate, yet the actual mechanisms underlying such functional relationships are still poorly understood. One such convincing example is the epigenetic inheritance of maternal behaviors in rats. In 2004, Michael Meaney and his colleagues showed that laboratory rats had two mothering styles. One mother type exhibited high level of licking and grooming behavior, while the other type showed very low levels of these behaviors. These alternative phenotypes seemed to follow simple Mendelian rules: adult females always exhibited the same behavior they experienced as pups. Surprisingly, cross fostering experiments

in which pups were switched at birth and so had an adoptive (environmental) mother as well as a biological (genetic) one suggested that the maternal care environment of female pups, not the genotype of the biological moms, determined their behavior as adults. This puzzling case of nongenomic inheritance was found to be driven by the high-grooming environment experienced by pups, which resulted in epigenetic modifications of the DNA that encodes the glucocorticoid receptor, a protein important for the regulation of stress-related behaviors in brains of vertebrates. Such modifications led to profound spatial and temporal changes in the brain expression patterns of this protein. These studies indicated that the rat genome potentially encodes two alternative maternal behaviors, and the one that is expressed is plastically dependent on a critical developmental window. The trait is then subsequently transferred across generations as a fixed trait as long as the maternal environment does not change (for example, by being switched at birth by an experimenter). Later investigations by the same group suggested that similar processes affect human behavior as well: similar DNA chemical modifications of the human version of the glucocorticoid receptor in the brain in response to early childhood abuse increased the likelihood of anxiety and suicidal behavior in these individuals as adults. These studies indicated that epigenetics is one of the key molecular processes that link genetic variations to environmental changes in the context of behavior (Zhang and Meaney 2010). This connection is further supported by many recent studies that have demonstrated a role for epigenetic processes in diverse behavioral phenotypes including learning, long-term memory, drug addiction, personality, and various neuropsychiatric disorders.

The fields of behavioral and evolutionary genetics are gaining momentum as a result of the technical and theoretical advancements in molecular genetics. This exciting progress should lead to a better understanding of how flexibility of behavior is maintained, how specific behaviors evolve, what role behavior plays in speciation, which genes are essential for normal neuronal functions, and what are the molecular bases for human behavioral pathologies.

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