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Forum

Comparative genomics and the roots of human behavior

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Advances in genomics provide tools to test whether similar behaviors in distinct species have statistically similar brain transcriptomic signatures. Here, we (a genomicist and a cognitive neuroscientist) suggest that these techniques can help cognitive scientists tackle some of the most pressing questions about the roots of human behavior.

Comparative studies have long been used by cognitive scientists to shed light on questions about the roots of human behavior by looking for comparable behaviors in diverse species. However, establishing similarities between disparate species is an ongoing challenge beset by problems, including the anthropomorphization of nonhuman behavior. Recent advances in comparative **genomics** (see Glossary) provide tools to test whether similar behaviors in distinct species have statistically similar brain transcriptomic signatures (see Box 1). Indeed, a succession of recent studies has highlighted similar transcriptomic profiles for vocal learning in songbirds and humans [1]; monogamy across vertebrates [2]; sociability in humans and bees [3]; and responses to social challenge across mice, fish, and bees [4].

This burgeoning field, which we refer to as 'comparative behavioral genomics' (Box 1; Figure 1), may help cognitive scientists overcome some of the challenges of comparative work by establishing whether behaviors that look the same 'on the outside' are really built from the same molecular components 'on the inside.' However, cognitive scientists address various types of questions about behavior, and, at present, it is not clear where comparative genomics can and cannot help. Here we highlight different types of questions that cognitive scientists typically care about and assess the extent to which comparative behavioral genomics can provide answers.

Questions about the ultimate, evolutionary roots of behavior

Tinbergen famously distinguished between questions about the proximate mechanisms underlying behavior and questions about its ultimate, evolutionary roots. A comparative approach is commonly used to tackle the latter and requires two steps: One must establish similarity between behaviors observed in distinct species, and one must establish **common descent**. Comparative behavioral genomics can help with the former but not the latter.

Establishing similarity

Common behaviors in disparate species can indicate evolutionarily old origins. Evidence of an instinct to turn toward conspecifics in zebrafish, for example, would raise the possibility that humans and zebrafish inherited this social orienting response from a common ancestor, meaning it is at least 400 million years old. A persistent challenge, however, concerns assessing whether common behaviors are really 'the same.'

One approach is to buttress similarity claims with evidence from multiple levels of biological organization: One might be more confident that social orienting is common to humans and zebrafish if it were underpinned by neural activity in the same regions. Problematically, although our knowledge of brain evolution is growing (e.g., [5,6]), and there is evidence that many elements of neural organization are well conserved [5,7], it is difficult to establish commonalities across species because brain anatomy can vary along multiple dimensions (number of layers, sulcal fold morphology, interconnectivity with other regions, etc. [8]). Although some tools (such as spatial transcriptomics) show promise for identifying molecular and neuroanatomical similarities (homologies), a gold standard comparison metric has not been firmly established.

Relative to brain and behavior, transcriptomic comparison is more precise because the number of available metrics for comparison is constrained (Box 1). That is, comparative behavioral genomics relies on quantifying the statistical similarity of the sequence of nucleotides in **genes** expressed in diverse species. Consequently, **genome**-level comparisons are a compelling source of evidence that can help build confidence in similarity claims.

Establishing common descent

A second, crucial step is to establish whether common behaviors are similar

Glossary

Common descent: a concept applicable when one species is the ancestor of two or more species. The more recent the ancestral population two species have in common, the more closely are they related.
Convergent evolution: the independent evolution of similar features in species. Convergent evolution creates structures that have similar form or function but were not present in the last common ancestor.
Gene: the basic unit of inheritance. Genes are passed from parents to offspring and contain the information needed to specify traits.
Gene expression: the process by which the information encoded in a gene's DNA is transcribed into mRNA. mRNA then directs the assembly of amino acids to form a protein molecule. Components of the cell read the sequence of the gene in groups of three bases. Each group of 3 bases (codon) corresponds to 1 of 20 different amino acids used to build a protein.
Genome: the entire set of genetic instructions found in a cell. The human genome comprises 23 pairs of chromosomes and a mitochondrial chromosome.
Genomics: refers to the study of the entire genome of an organism, whereas 'genetics' often refers to studies of heredity or the study of individual genes.
Orthologous genes: genes evolved from a common ancestral gene by speciation that usually retain a similar function in different species.

Box 1. Comparative behavioral genomics

Comparative behavioral genomics uses an analytical framework for calculating the statistical similarity of transcriptomic signatures of behavior in distinct species. A standard approach involves first comparing mRNA samples from individuals within a species to identify a list of genes that are differentially expressed ('transcribed') in the brains of individuals that exhibit the behavior of interest compared with a suitable control group. A list of these genes comprises a 'transcriptomic signature' of the behavior. For a cross-species comparison, this gene list is mined for **orthologous genes**. To achieve this, an algorithm is used to estimate the probability that two proteins come from mRNA sequences sufficiently similar that they are unlikely to be that similar by chance and therefore likely arise from orthologous genes. Comparative behavioral genomics thus quantifies the extent to which behaviors that appear the same are associated with the expression of common genes. For a more sophisticated analysis, one could use spatial transcriptomics to determine where in the brain common genes are expressed, thus providing insight into whether common transcriptomic signatures are present in common (i.e., analogous or putatively homologous) brain regions in disparate species.

by descent (i.e., 'conserved'). Social orienting, for example, could evolve independently in humans and zebrafish because of shared selection pressures, much like the **convergent evolution** of flight in insects, birds, and bats. Although different genomic signatures indicate likely convergent evolution, common signatures do not necessarily indicate that the behavior itself is conserved. Common signatures cannot discriminate between conservation and convergence, because evolution can independently converge on the same genomic signature for similar behavior in different species. For example, one study [3] found a common brain gene expression signature linked to sociability in honeybees and humans. First, they compared socially responsive and socially unresponsive bees to identify the brain **gene expression** profile of bee sociability. Second, they compared this gene expression signature with sociability-related human genomic and transcriptomic signatures identified by comparing brain gene expression profiles as well as sets of gene variants from samples of autistic and non-autistic people. Remarkably, they found common genomic signatures in humans and bees, which included genes related to GABAergic transmission and ion channels. However, because the last common ancestor of humans and bees was a flatworm with zero known social ability, these types of sociability probably evolved independently in humans and bees, though nature used common molecular mechanisms in both cases, thus suggesting the existence of common building blocks for social brains in different species. In the future, statistical techniques that consider known relationships between gene families, as well as constraints and mutational biases that may increase the chances of genetic convergence, may enable us to distinguish between convergent and conserved transcriptomic signatures. At present, this remains a challenge for the field.

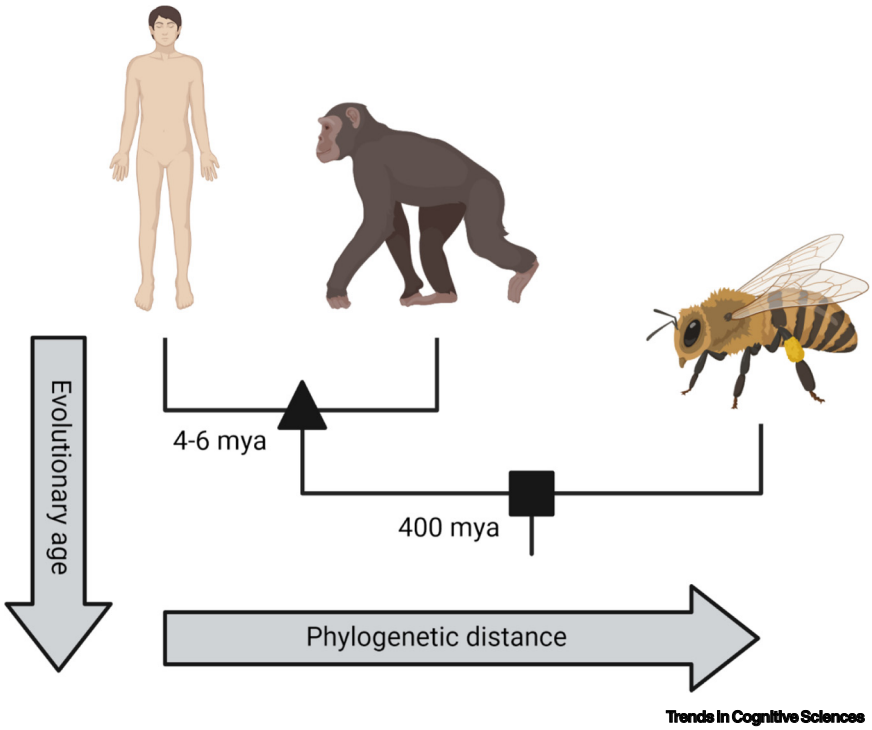

Figure 1. Evolutionary age of common instincts increases with phylogenetic distance. A comparative approach is often used to estimate the evolutionary age of a behavior. Evidence of social orienting in both humans and chimpanzees would raise the possibility that these species inherited this instinct from a common ancestor (denoted by the triangle), meaning that it is at least 4 million to 6 million years old. Evidence of the same instinct in honeybees would increase this age estimate to 400 million to 600 million years. Abbreviation: mya, million years ago. This figure was created using BioRender (https://biorender.com/).

Questions about proximate causes of behavior

Tinbergen also taught that questions about the proximate causes of behavior can be separated into those about ontogeny – how the behavior has developed during the lifetime of the individual – and questions about the proximate psychological and neural mechanisms – the processes happening in the brain when the behavior is expressed. Both types of questions can benefit from a comparative behavioral genomic approach because both types benefit from the identification of appropriate model organisms.

Laboratories that study the proximate psychological and neural mechanisms of human behavior typically interrogate brain

and behavior at a macroscopic level using tools such as magnetic resonance imaging and magnetoencephalography. This approach provides insight into neural systems and cognitive and behavioral mechanisms but leaves an explanatory gap with respect to genetic, molecular, and circuit-level mechanisms. Appropriate model organisms can help fill this explanatory gap [9].

Model organisms are equally important in understanding how behavior develops during a lifetime. Honeybee research, for example, has provided crucial insight into epigenetic factors that help explain how environments result in long-lasting behavioral modifications via changes in brain gene expression [10]. Model organisms are particularly useful here because it is nearly impossible with human studies to extract transcriptomic data from the living brain, sequence multiple individuals quickly and cheaply, and obtain high levels of control over environmental factors. Bees and vertebrate species such as stickleback fish [4] and deer mice [11] are especially useful if one is interested in behavior in naturalistic environments; otherwise, the traditional model genetic organisms, *Mus musculus, Danio rerio, Drosophila melanogaster,* and *Caenorhabditis elegans*, provide more sophisticated tools for neural and genetic manipulation.

Comparative behavioral genomics (Box 1) can help identify model organisms with signatures of behavior similar to those exhibited by humans. This approach can help us to choose appropriate model organisms for particular behaviors. Common transcriptomic signatures for sociability in humans and bees, but not in humans and zebrafish, for example, would promote bees as a good model for studying the proximate mechanisms and epigenetic factors underpinning sociability. Similarly, this comparative behavioral genomic approach could be used to select 'model clades' [12]. Because clades (groups of species with a common ancestor) feature diverse behaviors, they are particularly useful in understanding the relationship between neurobiological and behavioral evolution.

Concluding remarks

Advances in genomics provide tools to test whether similar behaviors in distinct species have statistically similar brain transcriptomic signatures. These comparisons can help build confidence in similarity claims by illustrating that behaviors that look the same 'on the outside' are built from the same molecular components 'on the inside.' Although comparative behavioral genomics cannot by itself tell us whether comparable behaviors in disparate species are similar by descent, this approach can help us more broadly identify appropriate model organisms for the interrogation of the epigenetic, molecular, and neural mechanisms underpinning particular behaviors.

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Declaration of interests

The authors have no interests to declare.

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