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Varieties of behavioral natural variation

Patrick T McGrath

Behavior is flexible at different timescales, modifiable by experience in the short term and by evolution in the long term. In order to understand how behavior evolves, we must both understand how trait differences between individuals are inherited and how a subset of these differences get fixed within a species' lineage. Work over the past few decades has shown that this will not be easy; the genetic basis of heritable behavioral differences between two individuals is typically complex, caused by multiple genetic variants of small effect. Here I describe how the underlying genetic networks impact the types of genetic variants that can be selected for by evolution.

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Introduction

Heritable differences in behavior are the substrate for evolutionary change. As such, there is considerable interest in understanding how genetic differences between two individuals can lead to differences in behavior. While a few early elegant examples linked segregating genetic changes in expression or function of a protein to a behavioral change [1–4], there are no obvious commonalities between these genes. While some trait differences are caused by single loci of large effect, many trait differences are caused by a complex combination of genetic changes distributed throughout the genome [5–7]. Genetic changes proposed to be responsible for behavioral adaptations along the human lineage seem to be similarly complex; coding changes [8,9], duplications [10••,11••,12], small noncoding RNA changes [13], cis-regulatory changes [14–16], and neural-specific alternative splicing changes [17] have all been linked to the evolution of human behavior. As causative variants continue to be identified [18••,19•,20,21•,22••,23], the challenge moves from cataloging these variants to understanding why or even whether they are preferred. Here I start to discuss some broad considerations that might help make sense of this complexity, using the more mature field of evolutionary developmental biology (evo-devo) as a guide.

Comparison and contrast between evolution of behavior and development

Two important principles, likely to be applicable to the genetic basis of all aspects of evolution, have emerged from the study of evo-devo. First, it has been argued that mutations with greater pleiotropic effect will have more deleterious effects on fitness [24,25]. Second, the genetic changes that can non-pleiotropically modify a biological trait are constrained by its underlying genes and gene networks [26]. For the case of morphological evolution, the underlying genetic pathways seem to favor modification of cis-regulatory elements controlling expression of highly conserved pleiotropic patterning genes [26]. However, the genes and genetic networks controlling behavior will be different from morphological development. As such, we should expect to identify different subset of causative genetic changes.

Development is determined by a robust genetic program. To a large extent, the shapes and colors of an organism are determined solely by its genome. In contrast, animal behavior is a result of interactions between not only a genetically encoded developmental program (which encodes the function and connections of the underlying nervous system), but also information about its rapidly changing environment, information about the current state of an organism (e.g. behavioral states and mood), and memories that encode information about an organism's previous experience (Figure 1). Each of these aspects of a nervous system can be modified to change behavior. Each is controlled by a different set of genes and gene families. These added layers of function likely account for at least some of the complexity in the genetic basis of behavioral differences. In other words, the study of the evolution of behavior is the study of at least four different aspects of organismal biology. To make headway in understanding how behavior evolves, we must consider each aspect of nervous system function independently. What genes and gene families control each of the underlying processes? I begin to do this here by focusing on sensory systems.

Evolution of sensory systems

Animals utilize multiple sensory modalities to gather information about their environment. Sight, taste, smell, touch, and hearing are the most familiar senses to humans, but different organisms encode different aspects of the environment depending on their lifestyle.

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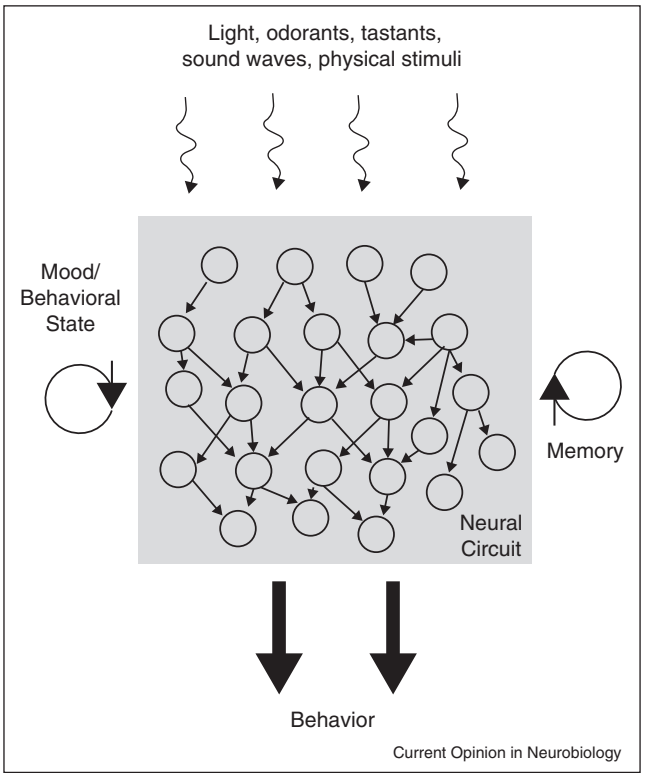
Figure 1



Schematic of processing carried out by a nervous system. A nervous system must process information about the environment, internal state, and memory into a coherent output. Each of these systems are controlled by a different set of genes and gene families, creating a different set of genetic substrates for natural selection to operate on.

Dedicated organs — eyes, noses, and mouths, for example — have evolved to facilitate the detection of particular stimulus. Different species do not detect the same set of stimuli, rather each species detects a subset of stimuli with different sensitivity. There are at least three drivers for evolution of sensory encoding.

An animal's environment is changing

Environment is heterogeneic, changing both spatially and temporally. For example, the amount of predators and prey in an environment changes over time, resulting in the loss and gain of some stimuli (e.g. odorants and pheromones released by other species in the vicinity). As a result there will be positive selection to detect novel stimuli and change the gain or sensitivity for existing stimuli. There will also be pressure, through positive selection and genetic drift, to lose the ability to sense stimuli that are no longer present in the new environment.

Animals only sense a subset of their environment

The exact set of stimuli that each organism senses is a small subset of the total environmental stimuli within an animal's environment. There are energetic costs associated with the ability to sense a particular cue — encoding and producing its sensory protein, dedicating sensory neurons for its detection, and/or building a sensory organ to house the sensory neurons. Consequently, there must be an associated selective advantage to sensing a particular stimulus, such as aiding in finding food, avoiding predators, or finding a mate. Since these selective forces are also evolving (e.g. an animal's choice of food could change), the exact subset of stimuli that are sense will be evolving as well.

Animals use sensory cues as proxies for other information

Finally, animals typically do not directly detect salient features of their environment, such as prey and predators. Rather they infer their existence based upon specific stimuli. For example, mosquitoes use carbon dioxide as an attractive cue to find prey. Carbon dioxide itself is not beneficial to the mosquitoes, in fact, it is toxic at high levels. Rather it signals the presence of a respiring organism, potentially a source for a blood meal. The salience of any given cue will also change through time, changing the selective pressure on the stimulus.

The genetic basis of sensory evolution

What is the genetic basis of sensory evolution? How do animals deal with the previously described evolutionary pressures to modify their sensory capacities? At this point it is useful to turn back to the principle of pleiotropy. In general, when pressure arises for an animal to modify its response to a single stimulus, it will be detrimental to change its response to other stimuli [24,25]. Sensory genes create a natural genetic substrate for this. In general, sensory genes are circumscribed, encoding proteins that sense a specific stimulus or small subset of stimulus. Modification of a single sensory gene can enable the loss or gain in sensitivity to a given stimulus, without impacting the animal's ability to sense another stimulus. For example, pigment opsins, which are responsible for light detection for tri-chromatic vision in primates, do not participate in detection of odors. This modularization of function seems to be further subdivided into biological traits. Separate opsin-like proteins are used for color vision, dim light vision, and entraining circadium rhythms [27].

Genomic data also support the role for evolution of sensory genes in evolution. They come from some of the fastest evolving gene families in metazoan genomes, characterized by high levels of gene loss, gene duplication, and functional evolution [28] (Figure 2). Recent shifts in environment, such as Drosophila sechellia's highly specialized use of the Morinda fruit as a food source, are correlated with changes in sensory gene repertoire [29]. Scans for evidence of positive selection have repeatedly found odorant receptors and taste

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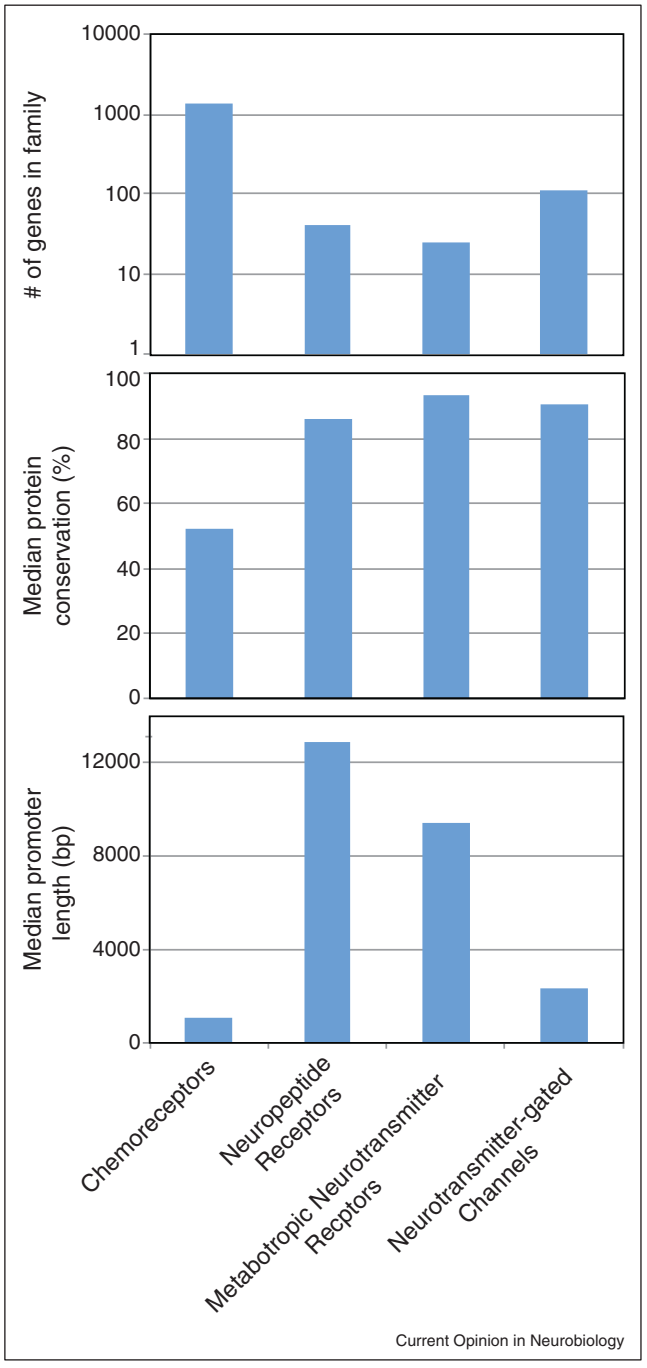
Figure 2



Genomic analysis of four gene families in *C. elegans*. Chemoreceptors come from large families that evolve rapidly (average homology is determined from best hit within the closely related *C. briggsae* species) compared to other neuronal genes. Neuromodulators, such as metabotropic neurotransmitter receptors and neuropeptide receptors, are highly conserved but expressed from large cis-regulatory regions (as determined by the distance to the next gene). The large regulatory regions create a genetic substrate for natural selection to modify behavior of an animal. These large upstream regions are atypical in *C. elegans*. For example, neurotransmitter-gated channels, which are also highly conserved, are expressed from much smaller upstream regions.

receptors to be enriched compared to other genes [30]. In addition, genetic variants within sensory genes have been linked to differences in abilities for mammals to smell particular odorants [20], taste bitter tastants [2,31], taste sweet [32•,33], or taste umami [34]. Genetic changes are also associated with differences in sensitivities to lights of different wavelengths [35] including infrared wavelength light [36,37••], differences in nematode sensitivities to oxygen [21•,23], and differences in *Drosophila* sensitivity to the insect repellant DEET [38•].

Evolution of sensory genes can be reproducible in response to a defined environmental shift

Classical work by Yokoyama has shown that evolution of opsin genes could be reproducible in response to changes in environmental light conditions [35]. Recent work on the nematode *Caenorhabditis elegans*, a small bacteriovore found in rotting fruit, supports the notion that sensory genes can be preferred genetic targets of natural selection in response to a change in environmental condition [22••]. In challenging environmental conditions, young *C. elegans* larvae can enter a hibernation-like state known as dauer [39]. This neuronally controlled decision results from the integration of a number of environmental stimuli, including conspecific population density, which is signaled through the release and detection of multiple pheromones [40]. Strains of *C. elegans* grown in the laboratory at high density for long periods of time, where pheromones accumulate to high levels, have become resistant to dauer-inducing pheromones [22••]. The genetic basis of the defect to one of the dauer-inducing pheromones was caused by deletions in chemoreceptor genes that specifically sensed this pheromone [22••]. These receptors were deleted independently from three different strains, suggesting that the potential genetic targets for specifically decoupling this pheromone from the decision to enter dauer seems to be limited to these pheromone receptors genes [22••].

This work supports the model that functional changes in sensory genes can be a preferred route of evolution. This further suggests that loss of sensory genes will not just be due to relaxation of purifying selection but rather positive selection to change an animal's response to an environment. Recent work on loss of function polymorphisms in humans suggests that deletions of odorant receptors in humans can also be caused by positive selection [41•]. At least nine deletions in odorant receptors are associated with signatures of recent positive selection.

Evolution of a metabotropic bioamine receptor — a connection between behavior state and sensory systems

Sensory information must be integrated with information about the internal states of an animal, which are also likely

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to be under evolutionary pressure. Additional work in *C. elegans* nicely illustrates this. Bendesky and colleagues identified a genomic region that affects the decision of when to leave a depleting food source in search of a novel source of food [18••]. While the exact genetic variant was not identified, it was shown to map nearby the tyra-3 gene, which encodes a G-protein-coupled receptor for the invertebrate norephinephrine-like neurotransmitters tyramine and octopamine [18••]. Increased expression of tyra-3 in a pair of sensory neurons was correlated with and sufficient to cause a decreased frequency of leaving the food source. The most parsimonious explanation of these data is that the causative mutation is a cis-regulatory change in tyra-3.

In this case, the genetic change seems to modify how an internal state of the animal affects behavior. Tyramine and octopamine are similar in structure to epinephrine and norepinephrine. These neurotransmitters regulate arousal systems in vertebrates, which tie into many different behavioral decisions. Similarly, levels of tyramine and octopamine could signal overall arousal level for the worm, which then ties into foraging decisions via tyra-3 activity in sensory neurons. Tyramine and octopamine regulate a number of *C. elegans* behaviors besides foraging [42,43], presumably in part though tyra-3 actions in other neurons, therefore, in cis-regulatory changes in tyra-3 are necessary to specifically decouple arousal from foraging. Functional changes in the TYRA-3 protein would result in greater pleiotropic effects, which in general should be deleterious to the organism.

Again, genomic data are consistent with a role for cis-regulatory changes in neuromodulatory genes (such as metabotropic neurotransmitter receptors and neuropeptide receptors). These genes are highly conserved, indicating that functional changes in these proteins are typically selected against (Figure 2). However, expression of these genes is controlled by large cis-regulatory regions that create a large genetic substrate to modify the deployment of these receptors (Figure 2).

Conclusion

Much work remains to understand the genetic basis of behavioral evolution. Here I analyze a few recently identified causative polymorphisms in the context of genomic information about the gene families that they modify. This analysis suggests that there are some general rules by which behavioral evolution proceeds. Future work will be required to identify and synthesize these rules into a coherent understanding of why so many types of genetic changes are utilized by evolution to modify behavior.

Acknowledgement

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