Title
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Permalink
https://escholarship.org/uc/item/0z82f8s6

Journal
Proceedings of the Annual Meeting of the Cognitive Science Society, 36(36)

ISSN
1069-7977

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Publication Date
2014

Peer reviewed

Cognitive Biology: Surprising Model Organisms for Cognitive Science

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Abstract

Cognitive biology refers to investigations of cognitive processes in a wide range of model organisms from bacteria to plants and animals. Although this research has generally been beyond the scope of mainstream cognitive science, I argue that cognitive science would benefit from integrating investigations into model organisms and focus on what can be learned from surprising model organisms—bacteria and invertebrates. Evolution is a highly conserved process, and the mechanisms developed in our common ancestors with these species provide the foundation for many of our cognitive activities. Since these organisms lack some of the complications that have evolved in us, research on them can help reveal key features of our cognitive mechanisms.

Keywords: Cognitive biology; model organisms; perception; decision making; memory and learning; sleep

Introduction

Biologists routinely conduct research on other species chosen to facilitate particularly productive investigation of the mechanisms operative in the species of primary interest, often humans. Often research focuses on organisms for which the last common ancestor occurred very early in phylogeny but that nonetheless exhibit a version of the phenomenon of interest. In contrast, most research in mainstream cognitive science investigates the target organism, humans. Comparative psychologists have extended cognitive approaches to other organisms, especially primates and other vertebrates. While there are important exceptions, this research has tended to draw upon cognitive science to inform studies of these other organisms, and has had limited impact on cognitive science itself. I follow the lead of Lyon (2006) in highlighting the potential for influence in the other direction—invoking research on other organisms to inform cognitive science. Instead of focusing on our phylogenetically closer relatives, as valuable as that is, I turn to organisms for which the last common ancestor is much more ancient—bacteria and invertebrates. My contention is that cognitive science has much to gain by following the lead of biologists in incorporating research on cognitive processes in our most distant relatives into mainstream research and theorizing. In particular, understanding the mechanisms from which our more elaborate cognitive mechanisms evolved can provide distinctive insight into the core principles employed in the mechanisms operative in us.

In the next section I explore what cognitive science can hope to gain from incorporating research on model organisms, emphasizing that the goal is not to show that the models exhibit exactly the same cognitive traits as the targets, but that they are informative about the mechanisms operative in the target system. Then, in the remainder of the paper, I provide examples of what has been learned about cognitive mechanisms from bacteria and invertebrates. There is not space to examine research on plants here, but for illuminating discussion illustrating the potential of plant research to inform cognitive science, see Garzon and Keijzer (2011).

The Advantages of Using Model Organisms

There are a number of reasons biologists choose to investigate model organisms (Ankeny & Leonelli, 2011). For most model organisms there are well developed breeding programs that have generated stable lineages with greatly reduced genetic variability, enabling researchers to perform replicable investigations on the mechanisms that generate the phenomenon of interest. Moreover, the research community that has coalesced around model organisms has often developed and calibrated a host of investigative tools that researchers can employ. But the reason that is most relevant to the investigation of cognitive traits is that mechanisms in model organisms typically are simpler variants of ones found in the target organisms, allowing researchers to discover the basic components of the mechanism. Evolution often proceeds through duplication of genes and the subsequent specialization of the duplicates. This can result in a more complex mechanism in subsequent organisms in which it is difficult to make interventions that reveal the key components of the mechanism underlying the phenomena.

While the advantages of using model organisms may seem most obvious in the study of the genes and neural systems, my focus is on how it can contribute to understanding the mechanisms of cognition. The investigation of genes and neural circuits can itself contribute to understanding cognitive mechanisms, as these serve as their components. In understanding cognition, though, the focus is on the information processing operations these components perform. And in fact neurobiologists studying individual cells and small circuits are increasingly employing cognitive vocabulary to describe these information-processing mechanisms.

In turning to model organisms to study cognition, there are two divergent strategies—focus on organisms phylogenetically closest to humans or on the simplest organisms in which versions or components of the cognitive operations can be found. Each has its advantages. Close phylogenetic neighbors (primates or mammals) perform cognitive activities that are in many cases very similar to those of humans, reducing the number of modifications or additions of operations needed to realize the human cognitive capacities. Investigating organisms more reflective of our more ancient ancestors, on the other hand, provides insights into the basic cognitive operations that evolution made available for building other cognitive systems.

One concern about construing more distantly related organisms, including bacteria and invertebrates, as models for cognitive science is that the activities in which these organisms engage may not be properly construed as *cognitive*. One can debate the scope of the term, but my strategy is to focus on activities, such as perceiving and acting, decision-making, learning and memory, which fall within the domain of cognitive science when performed by humans. The human version of these activities is clearly much more complex, but the goal is to understand the basic principles employed in the responsible mechanisms, and a focus on simpler mechanisms employed in species reflective of early ancestors can provide a basis for understanding the more complex mechanisms underlying human activities regarded as cognitive.

Underlying model organism research in general, and the extension to cognitive science, is the recognition that evolution is a process of descent with modification such that the most sophisticated mechanisms result from modification of simpler designs. Although no living organism is the predecessor of organisms in other extant species, if two extant species share a common ancestry (hence, are homologous) and one has undergone less modification in its descent, then by studying it researchers can hope to have access to a less complicated version of the responsible mechanism in the more heavily modified species.

There is compelling evidence that many of the mechanisms in invertebrates on which I focus are homologous either at the anatomical level or the molecular level to those in humans. The case is less clear with bacteria, which lack a nervous system, often viewed as the physical foundation for any cognitive activities. In some cases the proteins and chemical reactions they deploy in regulating their behavior have been conserved, but even when that is not the case, it is becoming clear that bacteria need to engage in many cognitive activities to regulate their behavior. The mechanisms that underlie these activities provide insight into the sorts of information-processing operations all organisms must perform in order to survive. In these cases, descent with modification may have preserved the basic capacities of the cognitive mechanisms while substituting different components. Insofar as the demands on the mechanism are related, examination of the models can still be informative.

Model Organisms for Cognitive Capacities

In this section I present results of research on mechanisms in bacteria and invertebrates that perform versions of information-processing activities that count as cognitive in humans. With each capacity my goal is not only to show that the model organisms exhibit a version of the capacity, but also to illustrate what has been learned from research on the model organisms to illustrate how such organisms can serve as informative model organisms for cognitive science. A common feature of many of these exemplars is that they reveal mechanisms that operate in ways different than cognitive scientists have proposed when trying to hypothesize how human cognition must work.

Perceiving and Acting

I begin with perceiving and acting, which are arguably the prerequisite capacities for all other ("higher") cognitive activities. These were the abilities Aristotle thought distinguished animals from plants (*De Anima* I.5) and were long thought to be easy to explain. Reasoning, the distinctively human capacity for Aristotle, was what was thought to pose the explanatory challenge. However, as research in cognitive science has proceeded, perceiving and moving have turned out to be among the more challenging capacities to explain, in part because sensory processing already integrates a great deal of information and in part because of the reciprocity of perception and action. These complexities, moreover, are already exhibited in bacteria. Different species of bacteria employ different sensors and different modes of locomotion, but in all cases information about stimuli and internal conditions is used to control the mode of locomotion as well as other activities.

Escherichia coli, rod-shaped bacteria approximately 2 μm in length, employ chemical sensors to gather information about a variety of chemicals in their environment and a single locomotor mechanism, a flagellum, to move through their environment. The flagellum consists of four filaments that extend several body lengths into the external medium and a relatively elaborate motor that can turn either clockwise or counterclockwise at speeds of approximately 100 Hz (Berg, 2004). When all four motors spin counterclockwise the filaments form a bundle that propels the bacteria forward. When one or more motors convert to clockwise movement, the corresponding filament leaves the bundle, resulting in the bacterium tumbling. Typically *E. coli* alternate between forward motion and tumbling, but activity at the sensors alters the frequency of performing the two actions. *E. coli* has five transmembrane methylated chemotaxis proteins (MCPs) located at the poles that serve as sensors. These proteins can each bind to different chemicals in the environment and when they do so the part of the protein on the cytoplasmic side phosphorylates or dephosphorylates the sensor kinase CheA. CheA in turn phosphorylates the response regulator CheY, which diffuses through the cytoplasm; if it reaches the switch on the flagellum motor it binds, causing the motor to rotate counterclockwise and the bacterium to move forward (Bourret & Stock, 2002).

What I have sketched so far may seem to be a fairly simple feedforward mechanism or "reflex", but there are at least three features of this mechanism that make it a more sophisticated information-processing mechanism. First, there is a slowly functioning feedback loop from CheA that serves to demethylate the MCPs, reducing their responsiveness. This has the effect that the mechanism only continues to send a signal to the motor when the stimulus is increasing (e.g., the bacterium is moving up a chemical gradient). As a result of non-linearities in the CheA response, the system responds not to the absolute value of the stimulus but to the ratio of the current stimulus to that received in the recent past (Yi, Andrews, & Iglesias, 2007), implementing a form of the Weber-Fechner psychophysical law (an effect still in search

of a mechanism in human psychophysics). Second, the response regulator CheY integrates inputs from all five types of MCPs (complicated by the fact that there are different numbers of individual MCPs of each type and that each of the 10,000 MCPs can be in one of 16 methylation states). Thus, CheY release is not a dumb "reflex" triggered from outside but depends on state of the information-processing mechanism. Third, although CheY is the only response regulator for a motor response, there are other response regulators regulating gene expression and metabolic activities. As Yamamoto, Hirao, Oshima et al. (2005) demonstrated, there is a good deal of crosstalk whereby outputs of individual sensory kinases affect other response regulators. Hence, the pathway from stimulation to locomotion is not insulated from activities elsewhere in the cell (nor *vice versa*).

The perception-action system of bacteria is, altogether, far from a simple feedforward system but involves a complex, integrated network. The ability of bacteria to process information so as to register changing levels of stimuli over many order of magnitude, to integrate different sources of information, and to use feedback from other mechanisms to modulate the response of the sensors makes it clear why bacterial researchers have adopted a cognitive framework (Ben Jacob, Shapira, & Tauber, 2006; Shapiro, 2007). The success of researchers in deciphering that mechanism, though, makes it a useful exemplar for researchers studying more complex mechanisms in multi-celled organisms.

In bacteria the information-processing operations are often diffused throughout the cell, making functional localization difficult. An advantage in turning to animals with nervous systems to study information processing is that distinct neurons perform different information processing operations, allowing researchers to more readily characterize these operations. Here again there are more model organisms available than cognitive scientists have taken advantage of. Olfaction is the animal variant of chemoreception, and fruit flies have provided a productive model in which to investigate it. Processing of olfactory stimuli begins with specialized olfactory receptor neurons (ORNs) that express protein receptors. The relatively small number of these receptors (62) in fruit flies makes it possible to identify the neurons in which they are expressed, the ligands they bind, and the coding system in which individual receptors contribute to the detection of many odors (Hallem & Carlson, 2006). The ORNs expressing a given receptor all converge on a small number of glomeruli where they have synapses with excitatory and inhibitory interneurons and neurons projecting to higher processing centers. While the gross anatomy of the brain is very different in flies and mammals, much of the cognitive architecture is conserved.

By investigating the fly's innate attraction to cider vinegar, Semmelhack and Wang (2009) were able to decipher the roles of individual glomeruli in generating behavioral responses. They found the coding for vinegar to be sparse—only 6 glomeruli responded. By selectively silencing the neurons innervating a given glomeruli, they showed that only two (DM1 and VA2), when silenced, affected the output response. Semmelhack and Wang were particularly interested in understanding why increasing concentrations of vinegar (as well as other odorants) results in reduced attraction or even repulsion. Their discovery of another glomeruli, DM5, that became activated with higher concentrations revealed a mechanism whereby one glomerulus opposes the signal from the other. Subsequently Root, Ko, Jafari et al. (2011) have shown that the outputs of sensory neurons reaching specific glomeruli are modulated by internal conditions such as starvation, which thus has the effect of altering the odor map. Other researchers have shown inter-glomeruli circuitry that provides gain control, quickly enhancing responses to weak inputs but preventing responses from saturating (Yaksi & Wilson, 2010).

Findings such as these reveal that sensory processing in bacteria and fruit flies is not simply stimulus driven but involves complex filtering and integration of information. These early-evolved mechanisms for processing sensory information in complex and sensitive ways were resources for evolution in developing the mechanisms that figure in our own perceptual processing and studying them can provide insight into the more complex mechanisms in us.

Decision making

In all organisms, perceptual and motor processes must be coordinated to enable decisions as to the actions to be performed given specific internal conditions and stimulation. Bacteria allow us to decipher the mechanism our earliest ancestors evolved to cope with the demands of their environment. Kuchina, Espinar, Çağatay et al. (2011) studied the decision process in *Bacillus subtilis,* a bacterial species in which, under stress conditions, some organisms form spores and others enter competency and take up extracellular DNA. Cognitive scientists often assume such decision-making will employ an interactive network with inhibitory connections implementing a winner-take-all competition between the regulators for the two activities. Kuchina et al., however, revealed that in *B. subtilis* decisions result from a molecular race in which the programs for the two behaviors proceed independently and whichever reaches the decision point first determines the behavior.

Briggman, Abarbanel, and Kristan's (2005) research on the medicinal leech likewise pointed to an alternative to winner-take-all computation in animals. Leeches need to make choices between various possible actions such as swimming, crawling, or feeding. The swimming-crawling decision is made in the 21 segmental ganglia in the nerve cord and these can be exposed so as to record selectively from the approximately 400 neurons in each ganglion. Briggman et al. examined responses to stimuli equally likely to elicit either swimming or crawling by recording from 144 neurons in a single ganglion. A plausible assumption is that the neurons that first exhibit the activity pattern predictive of one behavior or the other would be the decision neurons. If that is the case, hyperpolarizing or depolarizing these neurons should bias the decisions. But none of the neurons that

first exhibit differential responses could be biased, indicating none of them were responsible for the decision.

Turning to analytic techniques such as principal component analysis and linear discrimination, Briggman et al. found that before the decision could be detected in any individual neurons that first show differential responses, it is reflected in the collective activity of a different subpopulation of neurons. Among this population, they found one neuron, 208, whose manipulation could bias the production of swimming versus crawling behavior, leading researchers to conclude "this neuron plays a role in decision making." What is important is that 208 is not one of the neurons whose individual activity corresponded to the decision but rather a member of a population whose joint activity first revealed the decision, leading the researchers to interpret the behavior in terms of attractor dynamics. Like the research in *Bacillus*, the leech studies reveal an alternative to winner-take all competition that might be conserved in higher organisms including humans.

Learning and Memory

Part of what makes investigating information processing mechanisms challenging is that the mechanisms themselves change as a result of learning and memory. One objective of memory research is to determine what changes. As a result of their relative simplicity, invertebrates have proven a valuable model in which to seek specific loci of change. Although much of the research has focused on relatively simple learning tasks, such as habituation or classical conditioning, invertebrate learning exhibits many of the features that researchers have sought to explain in humans, such as the spacing effect identified by Ebbinghaus and the context sensitivity of memory and research on invertebrates is providing clues as to the mechanisms that can explain these features.

Kandel's (1976) pioneering research on habituation of the gill withdraw response in *Aplysia* revealed the signaling pathway involving cAMP, PKA, and CREB is involved in synaptic changes. This pathway is conserved across species. However, an even simpler organism, the nematode worm *C. elegans*, provides a basis for identifying the neural circuits in which changes occur. White, Southgate, Thomson et al. (1986) showed that each nematode contains 302 neurons and produced detailed maps of the chemical and gap junction connections between them. This provides a reference point for identifying the cells that are changed in learning. A productive line of research has taken advantage of the fact that when the petri dish in which worms are swimming is tapped, worms swim backwards for a brief distance, but quickly habituate if the tapping continues. Wicks and Rankin (1995) identified a circuit of five mechanosensory neurons and four pairs of interneurons that generated the behavior.

What is perhaps most interesting is that worms exhibit long-term memory (extending up to five days in worms that only live 15-20 days) for tap habituation, but only when the training is spaced. Massed training (lacking intervals between blocks) with the same number of taps failed to generate long-term memory (Ebrahimi & Rankin, 2007). By noting that worms with mutations in a glutamate receptor did not show long-term memory and that massed training resulted in a decrease in the receptor protein, the researchers localized the responsible mechanism to protein synthesis within the cell. As glutamate receptors are also implicated in mammalian long-term memory, this mechanism seems to be conserved and may explain the importance of spaced training in developing human long-term memories. Worms also exhibit another feature of human long-term memory—better recall when tested in the same conditions as learning occurred (Rankin, 2000). Determining the responsible mechanism in worms could help in identifying the mechanism responsible for the phenomenon in humans.

Using fruit flies as model organisms provides researchers a rich set of mutants whose specific impairments facilitate differentiating the mechanisms involved in the encoding, storage, and retrieval of long-term memories. In *Dunce* and *rutabaga*, two of the first memory mutants to be identified, the mutation affected the conserved cAMP pathway that had been implicated in Kandel's *aplysia* research. Finding cAMP expressed at elevated levels in Kenyon cells in mushroom bodies (MB), paired neuropils sometimes regarded as analogous to the vertebrate hypothalamus, initially pointed to these cells as the locus of memory storage and consolidation (Tully & Quinn, 1985). Subsequent research has led to revision of this model by revealing a wealth of additional mechanisms whose operations are involved in previously unrecognized phases in the development of long-lasting memories (Margulies, Tully, & Dubnau, 2005). One phase involves what has been called anesthesia resistant memory (ARM); unlike long-term memory (LTM), ARM is not affected by blocking protein synthesis or genetic manipulations of CREB in the cAMP mechanism. Whereas LTM requires spaced training over several hours, ARM appears quickly and is strengthened by subsequent training, whether massed or spaced. ARM was revealed by its absence in a different mutant, *radish*, which implicated a deficit in protein kinase C signaling as responsible (Folkers, Waddell, & Quinn, 2006). Research employing classical conditioning has revealed yet other phases in memory acquisition. Another mutant, *amnesiac*, has revealed *amnesiac*-dependent, anesthesia sensitive, middle-term memory (MTM). The time frame for MTM corresponds to the time frame in which flies can learn to reverse the stimulus associated with the aversive stimulus (Margulies et al., 2005). Fly research is here proving useful in expanding the taxonomy of types of long-term memory beyond that developed in the human literature.

Other research on flies has revealed the importance of looking beyond the initially identified locus in Kenyon cells. Silencing neurotransmission from Kenyon cells impairs memory retrieval but not acquisition (Dubnau, Grady, Kitamoto et al., 2001). On the other hand, silencing projection neurons from the Antennal Lobes (the locus of the glomeruli involved in odor perception) to the mushroom bodies and to the lateral horn, blocks acquisition, implicating them

in the encoding process. This differentiation of memory mechanisms provides a probative model to investigate in vertebrates, where it may well be conserved and expanded upon, although testing this remains difficult. In some cases, though, fly research has already helped elucidate the mechanism response for known human disorders. For example, a gene whose expression is altered in Down's Syndrome, Down's Syndrome Critical Region 1, is a homolog of the fly gene, *nebula*. Both under expression and overexpression of *nebula* in mushroom bodies impairs LTM (Chang, Shi, & Min, 2003).

Sleep

As a final example, I turn to a phenomenon that has not been much discussed in cognitive science to date, but that has significant import for cognition—sleep. Sleep has long been a puzzling phenomenon. Our abilities to perform cognitive tasks, including taking actions to avoid danger, are interrupted during sleep, but appropriate sleep episodes are required to perform wakeful cognitive activities effectively and to consolidate memories. Finding appropriate model organisms in which to investigate sleep can facilitate acquiring an understanding both of the function of sleep and the mechanisms that govern it.

Electrophysiological measures such as EEG have become the standard measures of human sleep. However, Hendricks, Finn, Panckeri et al. (2000) and Shaw, Cirelli, Greenspan et al. (2000) showed that fruit flies satisfy the very behavioral measures that were used to validate EEG measures of sleep: rapidly reversible sustained periods of quiescence in a preferred location with stereotyped posture while exhibiting increased arousal threshold. They also demonstrated that flies exhibit other characteristics of sleep found in mammals, including responses to caffeine and changes with aging. Moreover, in both flies and mammals, sleep is governed by two mechanisms: a homeostatic mechanism that registers sleep need and the circadian clock that regulates timing of sleep. As a result, flies like mammals will increase their sleep in response to periods of sleep deprivation but consolidate their sleep at night.

There are three major motivations to investigate sleep in flies. First, such research may help elucidate the underlying mechanisms. For example, having identified a mutant fly, *minisleep*, that sleeps only 4-5 hours, Cirelli, Bushey, Hill et al. (2005) localized the deficit in *Shaker* (a gene first identified by the leg shaking it induced in mutants). *Shaker* encodes for a part of a K^+ channel involved in repolarizing membranes after action potentials. Cirelli et al. suggested that this process "may be close to the core mechanism" of sleep (p. 1090). Koh, Joiner, Wu et al. (2008) provided further support for this claim when they discovered the sleep promoting factor SLEEPLESS, which enhanced K^+ channel activity. Wu, Joiner, Dean et al. (2010) showed that it acts by forming a complex with Shaker. These investigations point to modulation of K^+ channels as a likely conserved factor in controlling sleep.

Second, research on fruit flies has helped elucidate the connection between circadian rhythms and sleep. Much of our understanding of the mechanisms underlying circadian rhythms in animals was developed through investigations of flies and then identifying conserved and altered components in the mammalian mechanism (Bechtel, 2009). In relating the core circadian mechanism to sleep, mammalian research had proposed that transforming growth factor-α (TGF-α), an output from the circadian clock, regulates sleep by binding to an ErbB receptor. But demonstrating this was difficult as there are four members of the ErbB family in mammals. Since there is only one ErbB in flies, Foltenyi, Andretic, Newport et al. (2007) were able to demonstrate its role in regulating sleep and especially sleep consolidation, thereby confirming the role of TGF-α as part of the information-processing link between the circadian clock and sleep.

Third, research on flies may provide insight into how sleep affects memory encoding. Joiner, Crocker, White et al. (2006) localized the mechanisms controlling sleep in flies to the MB, which we noted above were also implicated in learning and memory. Not only is the locus shared, but Hendricks, Williams, Panckeri et al. (2001) demonstrated a role of cAMP-PKA-CREB pathway in sleep homeostasis (increased cAMP associated with increased quiescence and increased CREB bound during restoration from sleep deprivation) as well as in the generation of circadian rhythms. This is the same pathway discussed earlier as involved in memory encoding and these results suggest a possible link between sleep homeostasis and the neural reorganization involved in the transition from intermediate to long-term memories (Bushey & Cirelli, 2011). Although these results are all at the molecular level, the linkages at this level point to how sleep affects information-processing mechanisms.

Conclusions

I have only been able to introduce a small sample of the investigations of cognitive abilities in bacteria and invertebrates. Researchers have pursued inquiries both into a much broader range of species (for additional examples, see North & Greenspan, 2007) and additional cognitive activities, including those involved in distributed cognition (exhibited in both bacteria and insects). The examples provided, though, suggest the value of conducting cognitive research on model organisms—such research can help in identifying the information processing operations involved in our own more complex cognitive abilities. The key to the strategy is to identify simpler variants of the responsible mechanism in which the effects of manipulations of components of the mechanism can be more easily identified. The insights gained can help human researchers identify the conserved or analogous operations operative in the cognitive mechanisms found in humans.

References

Ankeny, R. A., & Leonelli, S. (2011). What's so special about model organisms? *Studies in History and Philosophy of Science Part A, 42*, 313-323.

Bechtel, W. (2009). Generalization and discovery by assuming conserved mechanisms: Cross species research on circadian oscillators. *Philosophy of Science, 76*, 762-773.

Ben Jacob, E., Shapira, Y., & Tauber, A. I. (2006). Seeking the foundations of cognition in bacteria: From Schrodinger's negative entropy to latent information. *Physica A-Statistical Mechanics and Its Applications, 359*, 495-524.

Berg, H. C. (2004). *E. coli in motion*. New York: Springer.

Bourret, R. B., & Stock, A. M. (2002). Molecular information processing: lessons from bacterial chemotaxis. *The Journal of Biological Chemistry, 277*, 9625-9628.

Briggman, K. L., Abarbanel, H. D. I., & Kristan, W. B. (2005). Optical imaging of neuronal populations during decision-making. *Science, 307*, 896-901.

Bushey, D., & Cirelli, C. (2011). From genetics to structure to function: exploring sleep in *Drosophila*. *International Review of Neurobiology, 99*, 213-244.

Chang, K. T., Shi, Y. J., & Min, K. T. (2003). The *Drosophila* homolog of Down's syndrome critical region 1 gene regulates learning: implications for mental retardation. *Proc Natl Acad Sci U S A, 100*, 15794-15799.

Cirelli, C., Bushey, D., Hill, S., Huber, R., Kreber, R., Ganetzky, B., & Tononi, G. (2005). Reduced sleep in *Drosophila* Shaker mutants. *Nature, 434*, 1087-1092.

Dubnau, J., Grady, L., Kitamoto, T., & Tully, T. (2001). Disruption of neurotransmission in Drosophila mushroom body blocks retrieval but not acquisition of memory. *Nature, 411*, 476-480.

Ebrahimi, C. M., & Rankin, C. H. (2007). Early patterned stimulation leads to changes in adult behavior and gene expression in C. elegans. *Genes, Brain and Behavior, 6*, 517-528.

Folkers, E., Waddell, S., & Quinn, W. G. (2006). The *Drosophila* radish gene encodes a protein required for anesthesia-resistant memory. *Proc Natl Acad Sci U S A, 103*, 17496-17500.

Foltenyi, K., Andretic, R., Newport, J. W., & Greenspan, R. J. (2007). Neurohormonal and neuromodulatory control of sleep in *Drosophila*. *Cold Spring Harbor Symposia on Quantitative Biology, 72*, 565-571.

Garzon, P. C., & Keijzer, F. (2011). Plants: Adaptive behavior, root-brains, and minimal cognition. *Adaptive Behavior, 19*, 155-171.

Hallem, E. A., & Carlson, J. R. (2006). Coding of odors by a receptor repertoire. *Cell, 125*, 143-160.

Hendricks, J. C., Finn, S. M., Panckeri, K. A., Chavkin, J., Williams, J. A., Sehgal, A., & Pack, A. I. (2000). Rest in *Drosophila* Is a Sleep-like State. *Neuron, 25*, 129-138.

Hendricks, J. C., Williams, J. A., Panckeri, K., Kirk, D., Tello, M., Yin, J. C. P., & Sehgal, A. (2001). A non-circadian role for cAMP signaling and CREB activity in *Drosophila* rest homeostasis. *Nature Neuroscience, 4*, 1108-1115.

Joiner, W. J., Crocker, A., White, B. H., & Sehgal, A. (2006). Sleep in *Drosophila* is regulated by adult mushroom bodies. *Nature, 441*, 757-760.

Kandel, E. R. (1976). *Cellular basis of behavior: An introduction to behavioral neurobiology*. San Francisco: W. H. Freeman.

Koh, K., Joiner, W. J., Wu, M. N., Yue, Z., Smith, C. J., & Sehgal, A. (2008). Identification of SLEEPLESS, a Sleep-Promoting Factor. *Science, 321*, 372-376.

Kuchina, A., Espinar, L., Çağatay, T., Balbin, A. O., Zhang, F., Alvarado, A., Garcia-Ojalvo, J., & Süel, G. M. (2011). Temporal competition between differentiation programs determines cell fate choice. *Molecular Systems Biology, 7*.

Lyon, P. (2006). The biogenic approach to cognition. *Cognitive Processing, 7*, 11-29.

Margulies, C., Tully, T., & Dubnau, J. (2005). Deconstructing memory in *Drosophila*. *Current Biology, 15*, R700-R713.

North, G., & Greenspan, R. J. (2007). *Invertebrate neurobiology*. Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory Press.

Rankin, C. H. (2000). Context conditioning in habituation in the nematode *Caenorhabditis elegans*. *Behavioral Neuroscience, 114*, 496-505.

Root, C. M., Ko, K. I., Jafari, A., & Wang, J. W. (2011). Presynaptic facilitation by neuropeptide signaling mediates odor-driven food search. *Cell, 145*, 133-144.

Semmelhack, J. L., & Wang, J. W. (2009). Select *Drosophila* glomeruli mediate innate olfactory attraction and aversion. *Nature, 459*, 218-223.

Shapiro, J. A. (2007). Bacteria are small but not stupid: cognition, natural genetic engineering and socio-bacteriology. *Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences, 38*, 807-819.

Shaw, P. J., Cirelli, C., Greenspan, R. J., & Tononi, G. (2000). Correlates of sleep and waking in *Drosophila melanogaster*. *Science, 287*, 1834-1837.

Tully, T., & Quinn, W. G. (1985). Classical conditioning and retention in normal and mutant D*rosophila melanogaster*. *J Comp Physiol A, 157*, 263-277.

White, J. G., Southgate, E., Thomson, J. N., & Brenner, S. (1986). The structure of the nervous system of the nematode *Caenorhabditis elegans*. *Philosophical Transactions of the Royal Society of London. B, Biological Sciences, 314*, 1-340.

Wicks, S. R., & Rankin, C. H. (1995). Integration of mechanosensory stimuli in *Caenorhabditis elegans*. *Journal of Neuroscience, 15*, 2434-2444.

Wu, M. N., Joiner, W. J., Dean, T., Yue, Z., Smith, C. J., Chen, D., Hoshi, T., Sehgal, A., & Koh, K. (2010). SLEEPLESS, a Ly-6/neurotoxin family member, regulates the levels, localization and activity of Shaker. *Nature Neuroscience, 13*, 69-75.

Yaksi, E., & Wilson, R. I. (2010). Electrical coupling between olfactory glomeruli. *Neuron, 67*, 1034-1047.

Yamamoto, K., Hirao, K., Oshima, T., Aiba, H., Utsumi, R., & Ishihama, A. (2005). Functional characterization in vitro of all two-component signal transduction systems from *Escherichia coli*. *Journal of Biological Chemistry, 280*, 1448-1456.

Yi, T. Ä., Andrews, B. W., & Iglesias, P. A. (2007). Control analysis of bacterial chemotaxis signaling. In B. R. C. Melvin I. Simon & C. Alexandrine (Eds.), *Methods in Enzymology* (Vol. Volume 422, pp. 123-140): Academic Press.