REFERENCES

1. Vega, G.C., and Wiens, J.J. (2012). Why are there so few fish in the sea? Proc. R. Soc. B. *279*, 2323–2329.
2. Salzburger, W. (2018). Understanding explosive diversification through cichlid fish genomics. Nat. Rev. Genet. *19*, 705–717.
3. Matschiner, M., Hanel, R., and Salzburger, W. (2010). Phylogeography and speciation processes in marine fishes and fishes from large freshwater lakes. In Phylogeography: Concepts, Intraspecific Patterns and Speciation Processes, D.S. Rutgers, ed. (Nova Science Publishers), pp. 1–29.
4. Rocha, L.A., and Bowen, B.W. (2008). Speciation in coral-reef fishes. J. Fish Biol. *72*, 1101–1121.
5. Hench, K., Vargas, M., Höppner, M.P., McMillan, W.O., and Puebla, O. (2019). Inter-chromosomal coupling between vision and pigmentation genes during genomic divergence. Nat. Ecol. Evol. *3*, 657–667.
6. Puebla, O., Birmingham, E., and Guichard, F. (2008). Population genetic analyses of *Hypoplectrus* coral reef fishes provide evidence that local processes are operating during the early stages of marine adaptive radiations. Mol. Ecol. *17*, 1405–1415.
7. Puebla, O., Bermingham, E., Guichard, F., and Whiteman, E. (2007). Colour pattern as a single trait driving speciation in *Hypoplectrus* coral reef fishes? Proc. R. Soc. B. *274*, 1265–1271.
8. Fischer, E.A. (1980). Speciation in the hamlets (*Hypoplectrus*: Serranidae) - a continuing enigma. Copeia *1980*, 649–659.
9. Thresher, R.E. (1978). Polymorphism, mimicry, and the evolution of the hamlets (*Hypoplectrus*, Serranidae). Bull. Mar. Sci. *28*, 345–353.
10. Puebla, O., Bermingham, E., and Guichard, F. (2012). Pairing dynamics and the origin of species. Proc. R. Soc. B *279*, 1085–1092.
11. Fischer, E.A. (1980). The relationship between mating system and simultaneous hermaphroditism in the coral reef fish, *Hypoplectrus nigricans* (Serranidae). Animal Behav. *28*, 620–633.
12. Malinsky, M., Challis, R.J., Tyers, A.M., Schiffels, S., Terai, Y., Ngatunga, B.P., Miska, E., Durbin, R., Genner, M.J., and Turner, G.F. (2015). Genomic islands of speciation separate cichlid ecomorphs in an East African crater lake. Science *350*, 1493–1498.
13. Rennison, D.J., Owens, G.L., Heckman, N., Schluter, D., and Veen, T. (2016). Rapid adaptive evolution of colour vision in the threespine stickleback radiation. Proc. R. Soc. B. *283*, 20160242.
14. Singh, A.P., and Nüsslein-Volhard, C. (2015). Zebrafish stripes as a model for vertebrate review colour pattern formation. Curr. Biol. *25*, R81–R92.
15. Robertson, D.R. (2013). Who resembles whom? Mimetic and coincidental look-alikes among tropical reef fishes. PLoS One *8*, e54939.
16. Santos, M.E., Baldo, L., Gu, L., Boileau, N., Musilova, M., and Salzburger, W. (2016). Comparative transcriptomics of anal fin pigmentation patterns in cichlid fishes. BMC Genomics *17*, 712.
17. Saenko, S.V., Marialva, M.S.P., and Beldade, P. (2011). Involvement of the conserved Hox gene Antennapedia in the development and evolution of a novel trait. EvoDevo *2*, 9.
18. Mattar, P., Ericson, J., Blackshaw, S., and Cayouette, M. (2015). A conserved regulatory logic controls temporal identity in mouse neural progenitors. Neuron *85*, 497–504.
19. Cruickshank, T.E., and Hahn, M.W. (2014). Reanalysis suggests that genomic islands of speciation are due to reduced diversity, not reduced gene flow. Mol. Ecol. *23*, 3133–3157.
20. Puebla, O., Bermingham, E., and McMillan, W.O. (2014). Genomic atolls of differentiation in coral reef fishes (*Hypoplectrus* spp., Serranidae). Mol. Ecol. *23*, 5291–5303.

Learning and Memory: Mind over Matter in *C. elegans*

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The capacity to respond to adverse conditions is key for animal survival. Research in the nematode *Caenorhabditis elegans* demonstrates that retrieval of aversive memories, stored within sensory neurons, is sufficient to induce a protective systemic stress response that improves fitness.

Does the mind have the power to control systemic physiological processes? For example, could enhanced conscious awareness, through the practice of meditation, help us to relieve pain? In 1863, geologist Sir Charles Lyell postulated that the mind's ability to control body physiology, termed mind over matter, is a *bona fide* function that emerged as brains expanded in size over evolutionary time [1]. In this issue of *Current Biology*, a new study by Eliezer and colleagues [2] suggests that even the free-living soil nematode *Caenorhabditis elegans*, with its 302-neuron nervous system, may be endowed with the capacity to modify its physiology merely by recalling past experiences.

Like most animals, *C. elegans* must adjust its behavior and physiology in response to dire conditions. When food resources are limited, protective programs, which enhance somatic maintenance and repress reproductive development, are activated [3]. These systemic stress-induced pathways are thought to act, in part, through transcription of genes that promote stress resistance, fat metabolism, pathogen protection, and entry into a protective developmental state called dauer. Many of these transcriptional events are mediated by the DAF-16/FOXO forkhead transcription factor [4], which rapidly translocates from the cytoplasm to the nucleus following exposure to stressful conditions [5]. Activation of these transcriptional programs can take anywhere from minutes to hours. It would therefore be advantageous for *C. elegans* to have the ability to predict and prepare in advance for impending adversity. Associative learning is a mechanism that could underlie such an early warning system, predicting future events based on

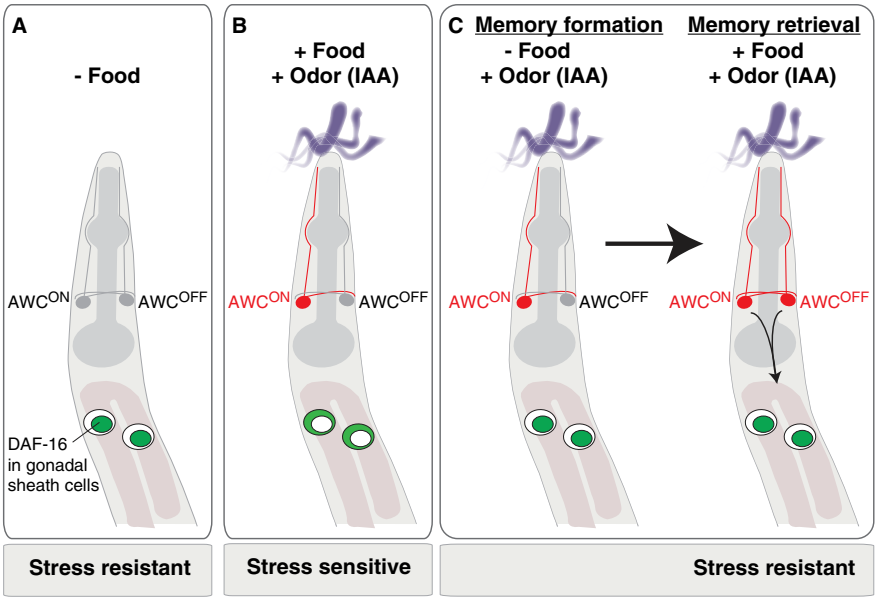

Figure 1. Evoking stressful memories allows animals to improve fitness to environmental challenges.
(A) Starvation results in DAF-16/FOXO nuclear translocation, conferring stress resistance. (B) In well-fed animals, DAF-16 is excluded from the nucleus, and animals are sensitive to stress. Independently, exposure to IAA results in AWC^{ON} activation. (C) During training (left), starvation and IAA are paired. Later exposure to IAA, even in the presence of food, results in activation of both AWC neurons, DAF-16 nuclear translocation and stress resistance.

past experiences. However, whether long-lasting memories can directly affect systemic physiological processes is not well understood.

To study mechanisms by which starvation-related memories are formed and retrieved, and how these memories might assist *C. elegans* in preparing for looming environmental challenges, Eliezer and colleagues developed and studied a simple associative memory paradigm [2]. Animals facing starvation were conditioned with the odorant isoamyl alcohol (IAA), and then allowed to recover for several hours in the presence of food and without IAA (Figure 1). Naïve *C. elegans* are attracted to IAA; however, the authors showed that pairing IAA with starvation dramatically changes preference to this odorant. Indeed, trained animals learn to avoid IAA, indicating generation of an aversive associative memory between starvation and IAA.

Next, the authors sought to determine whether evoking aversive memories, in the absence of stressful insults, is sufficient to induce a systemic stress response. To do so, they developed an impressive assay that allows observation of memory retrieval by following nuclear accumulation of GFP-tagged DAF-16 [2]. Remarkably, exposure of trained animals to IAA, even in the presence of food, is sufficient to induce rapid nuclear translocation of DAF-16 (Figure 1), followed by induction of DAF-16-dependent stress-response gene expression. Furthermore, the authors directly demonstrated that anticipating adverse conditions confers a survival advantage. *C. elegans* are sensitive to high temperatures, and prolonged exposure to temperatures above 30°C results in death [6]. Importantly, a short exposure to IAA before such heat treatment significantly increases survival of odor-trained, but not mock-trained, animals (Figure 1). Together, these observations suggest that the mere retrieval of a memory may directly affect physiology, to confer a fitness advantage in the face of harsh conditions.

DAF-16 nuclear accumulation is initially observed in gonadal sheath cells, before progressing to other somatic tissues. It has been previously shown that to cope with starvation, *C. elegans* enters a protective adult reproductive diapause (ARD) state that is reversible upon food availability [7]. As the gonadal sheath cells are necessary for germ-line development [8], it is plausible that DAF-16 nuclear accumulation serves for ARD initiation [9]. Subsequent DAF-16 nuclear accumulation in all other tissues is likely required for comprehensive systemic resistance to stress.

Eliezer and colleagues then aimed to identify the cells comprising the associative memory engram [10], i.e. the set of cells that are activated during the aversive learning paradigm and that are used for memory formation and retrieval. *C. elegans* is an attractive model to address such questions, as all synaptic connections between its 302 neurons are mapped [11], allowing functional assignment of circuits to specific behaviors [12]. Furthermore, the transparent cuticle allows the use of optical tools to record or modulate neuronal activities in intact animals. IAA is sensed by a pair of olfactory neurons designated AWC^{ON} and AWC^{OFF} that are wired to generate attractive behavior [13]. These neurons are generally similar in shape and activity, but exhibit differences in gene expression that are thought to reflect different sensitivities to odorants [13]. Remarkably, optogenetic activation of either AWC neuron is sufficient to induce DAF-16/FOXO nuclear accumulation in trained animals, but not naïve animals [2].

Unlike odor-responsive cells in other animals, where individual olfactory neurons express a single type of odorant receptor and distinct patterns of sensory neuron activation allow discrimination of a vast range of odors [14], AWC neurons express many odorant receptors and respond to a host of odor cues [13]. Thus, it is possible that memory of starvation–IAA pairing could be retrieved by exposure to a different AWC-sensed odorant. Supporting this idea, Eliezer and colleagues demonstrate that following pairing of IAA with starvation, introducing trained animals to other AWC-sensed odorants is sufficient to evoke the stress response [2]. This lack of discrimination seems somewhat surprising, as it could lead, at least in principle, to false alarms. However, it is possible that this result reflects an underlying logic of the *C. elegans* olfactory system, in which odors sensed by a common cell are likely to co-exist in naturally occurring, ecologically relevant settings. Indeed, such a design would greatly increase the

sensitivity of the system, as appropriate behavioral responses (attraction or avoidance) would be elicited by activation of a large number of redundant odorants.

How are memory formation and retrieval organized in AWC neurons? Although both AWC^{ON} and AWC^{OFF} neurons can sense IAA [15], recording of mock-trained animals expressing a genetically-encoded calcium indicator, and treated with IAA, showed enhanced responses in AWC^{ON} compared to AWC^{OFF} neurons. However, in odor-trained animals, the AWC^{OFF} response was modulated and became significantly more sensitive to IAA [2]. Furthermore, Eliezer and colleagues used genetic tools for transient neuronal inhibition during either memory-training or memory-retrieval sessions. While AWC^{ON} inhibition during training prevents formation of starvation-memories; its inhibition during the subsequent challenge has no effect on induction of the stress response. Conversely, AWC^{OFF} inhibition during the challenge, but not during the training session, completely blocks memory retrieval and stress-response induction [2]. Based on these observations, the authors conclude that AWC^{ON} is the main sensor of IAA and that its activity is required for memory formation, while AWC^{OFF} is recruited following training to store and retrieve the memory.

Although the downstream mechanisms by which these memory engram cells induce systemic stress responses is still largely unclear, the authors provide evidence that serotonin secretion from two head neurons can mediate the rapid systemic nuclear translocation of DAF-16/FOXO [2]. Interestingly, incubation of trained animals with exogenous serotonin was sufficient for memory retrieval. This suggests that cells situated downstream of the serotonergic head neurons are primed to sense serotonin following the IAA-training session. It will be fascinating to decipher how evoked memories are spread from the nervous system to the target tissues to generate a systemic protective response.

In sum, Eliezer *et al.* show that evoking stressful memories, stored within individual sensory neurons, allows animals to anticipate upcoming dire conditions, giving animals a head start to initiate protective responses throughout the body that ultimately increase fitness. It seems, therefore, that even *C. elegans* has learned to control matter with its mind.

REFERENCES

1. Lyell, C.S. (1914). The Geological Evidence of the Antiquity of Man (London: J.M. Dent & Sons Ltd).
2. Eliezer, Y., Deshe, N., Hoch, L., Iwanir, S., Pritz, C.O., and Zaslaver, A. (2019). A memory circuit for coping with impending adversity. Curr. Biol. *29*, 1573–1583.
3. Kirkwood, T.B. (2005). Understanding the odd science of aging. Cell *120*, 437–447.
4. Murphy, C.T. (2006). The search for DAF-16/FOXO transcriptional targets: approaches and discoveries. Exp. Gerontol. *41*, 910–921.
5. Henderson, S.T., and Johnson, T.E. (2001). daf-16 integrates developmental and environmental inputs to mediate aging in the nematode Caenorhabditis elegans. Curr. Biol. *11*, 1975–1980.
6. Lithgow, G.J., White, T.M., Hinerfeld, D.A., and Johnson, T.E. (1994). Thermotolerance of a long-lived mutant of Caenorhabditis elegans. J. Gerontol. *49*, B270–B276.
7. Angelo, G., and Van Gilst, M.R. (2009). Starvation protects germline stem cells and extends reproductive longevity in C. elegans. Science *326*, 954–958.
8. McCarter, J., Bartlett, B., Dang, T., and Schedl, T. (1997). Soma-germ cell interactions in Caenorhabditis elegans: multiple events of hermaphrodite germline development require the somatic sheath and spermathecal lineages. Dev. Biol. *181*, 121–143.
9. Ratnappan, R., Amrit, F.R., Chen, S.W., Gill, H., Holden, K., Ward, J., Yamamoto, K.R., Olsen, C.P., and Ghazi, A. (2014). Germline signals deploy NHR-49 to modulate fatty-acid beta-oxidation and desaturation in somatic tissues of C. elegans. PLoS Genet. *10*, e1004829.
10. Tonegawa, S., Liu, X., Ramirez, S., and Redondo, R. (2015). Memory engram cells have come of age. Neuron *87*, 918–931.
11. White, J.G., Southgate, E., Thomson, J.N., and Brenner, S. (1986). The structure of the nervous system of the nematode Caenorhabditis elegans. Philos. Trans. R. Soc. Lond. B. Biol. Sci. *314*, 1–340.
12. Bargmann, C.I., and Marder, E. (2013). From the connectome to brain function. Nat. Methods *10*, 483–490.
13. Bargmann, C.I. (2006). Chemosensation in C. elegans. WormBook, 1–29.
14. Bushdid, C., Magnasco, M.O., Vosshall, L.B., and Keller, A. (2014). Humans can discriminate more than 1 trillion olfactory stimuli. Science *343*, 1370–1372.
15. Troemel, E.R., Sagasti, A., and Bargmann, C.I. (1999). Lateral signaling mediated by axon contact and calcium entry regulates asymmetric odorant receptor expression in C. elegans. Cell *99*, 387–398.

Actin: Post-translational Modification of Actin Linked to Formin Inhibition

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Actin undergoes several forms of post-translational modifications that play roles in normal physiological processes and pathological states. A new study reveals that a complex between lysine-acetylated actin and cyclase-associated protein inhibits the formin INF2 by enhancing intramolecular inhibitory interactions in this protein.

Actin is the most abundant protein in the cytoplasm of most human cells and is implicated in essential activities, ranging from endocytosis and exocytosis to organelle trafficking and cell motility. The cellular pool of actin is roughly evenly divided between monomeric and filamentous forms. Several factors