Worm 2:2, e22725; April/May/June 2013; © 2013 Landes Bioscience

Entwined engrams

The evolution of associative and non-associative learning

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The nematode *Caenorhabditis elegans* displays a surprisingly sophisticated behavioral repertoire that includes the utilization of both associative and non-associative forms of learning. Elucidating the molecular basis of learning remains a fundamental, yet daunting, challenge of modern neuroscience. In Pereira and van der Kooy (ref. 2), we described the use of a two input—two output stimuli system to dissociate between associative and non-associative learning and between memory acquisition and retrieval processes. Briefly, one finding indicated that after training with the odorant isoamyl alcohol (IsoA), we could preferentially retrieve either associative or non-associative memory with a choice of either a benzaldehyde (Bnz) or IsoA retrieval stimulus, respectively. Here, we describe how that apparently enigmatic molecular cross wiring of the two forms of memory examined could represent an evolutionary relic of the ancient divergence between non-associative and associative learning. In addition, we extrapolate on the utility and subtleties of using such a system to dissociate and decipher the components of memory in *C. elegans*.

Keywords: evolution of learning, associative learning, olfactory adaptation, habituation, *C. elegans* behavior

Submitted: 09/30/2012

Revised: 10/19/2012

Accepted: 10/30/2012

http://dx.doi.org/10.4161/worm.22725

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Commentary to: Pereira S and van der Kooy D. Two forms of learning following training to a single odorant in Caenorhabditis elegans AWC neurons. J Neurosci 2012; 32:9035-44; PMID:22745502; http://dx.doi.org/10.1523/JNEUROSCI.4221-11.2012.

"Know then, that there is nothing more lofty, nor more powerful, nor more healthy, nor more useful later on in life than some good memory…If he gathers many such memories in his life, a man is saved from it all."[1] While not its intended audience, Dostoevsky's sagacious advice from *The Brothers Karamazov* may be equally useful for the soil dwelling nematode worm *Caenorhabditis elegans*. The ability to modify behavior according to the dictates of experience, in contrast to fixed, intrinsic behavioral patterns, provides an opportunity to act in a more optimal manner in terms of foraging and successful avoidance of predation.

Our work in Pereira and van der Kooy attempted to dissect the processes underlying this ability to encode, store and retrieve memory; among the most enigmatic of natural phenomena.[2] With a fixed behavioral output, generations of *C. elegans* undergoing natural selection would be required to fix a new optimal pattern, while in contrast, behavioral plasticity can occur with memories forming on the order of minutes. This vast improvement in behavioral adaptation has been highlighted previously and underlies the common paradigm regarding the evolution of learning.[3] In addition, recent memory is more likely to be relevant to the current environmental situation encountered by a worm than fixed behavioral patterns that may have evolved in a distant past under radically different environmental pressures.

Evolutionary adaptation has been famously described as the great "tinkerer", where sophisticated memory mechanisms are assembled ad hoc from changes to more primitive, ancestral mechanisms already in place.[4] Such a notion would lead one to believe that the more complex associative learning would be built upon non-associative learning pathways. Yet Moore (2004) has pointed out that the literature has continued to treat psychologically distinct forms of memory as "special creations" and has failed to appreciate the gradual evolutionary process through which more sophisticated forms

of learning and memory may appear in a manner analogous to morphological features.[5] Moore consequently outlines one of the most wide-ranging attempts to generate a systematic phylogeny of learning. Significantly, such a process may result in cases with either intermediate forms of learning and instances where forms of memory are molecularly intertwined as a relic of the process of evolutionary divergence. We posit that such an instance has been uncovered in our work.

Arguably, the most fundamental distinction that would have had to occur in the evolutionary history of learning is that between non-associative, in our case habituation, and associative learning (likely Pavlovian conditioning). Non-associative learning refers to modification of a behavior to a stimulus that is not dependent on pairing that stimulus with another stimulus.[6] Habituation is a form of non-associative learning is which the behavioral modification is a reduced response to a stimulus that is not a result of motor or sensory fatigue and is sensitive disruption by presentation of another strong stimulus (dishabituation). In contrast, associative learning refers to forms of learning where modification of the behavior to a conditioned stimulus (CS) is dependent on its prediction of the occurrence of a salient unconditioned stimulus (US). Habituation necessitates a mechanism that is far simpler than associative learning, since it only requires a mechanism that changes with repeated presentation of a single stimulus. On the other hand, associative learning posits a mechanism where only the contingent presentation of conditioned and unconditioned stimulus leads to formation of the engram. This suggests that non-associative learning most likely arose first in evolutionary history. Habituation provides the organism with an advantage through prevention of an apparently unnecessary behavioral response that may prevent a more optimal behavior. For example, in *C. elegans* repeated mechanical disturbance (tap) illicits a reversal and omega turn response.[7] Without a habituative mechanism, such a response in a physically truculent environment would prevent *C. elegans* from foraging. Yet while such a mechanism facilitates foraging through elimination of detrimental behavior, it does not actually provide information regarding or direct *C. elegans* toward a food source. Associative learning, in contrast, presents worms with the ability to directly seek out stimuli whose correlation with food has been empirically validated. It is difficult to overstate the advantage that an organism would gain over its competitors by possession of such a mechanism. Indeed, it has been suggested that the emergence of primitive mechanisms of associative learning was one of the underlying causes of the Cambrian explosion since it enabled it possessors to exploit previously untapped resources.[8]

In Pereira and van der Kooy[2] we employed a two training-two retrieval stimulus system to dissect memory both in terms of memory phase (acquisition vs. retrieval) and memory type (associative vs. non-associative learning) through a *C. elegans* olfactory adaptation assay. The two stimuli we employed in both training and retrieval, benzaldehyde (Bnz) and isoamyl alcohol (IsoA) (IUPAC: 3methylbutanol), are defined olfactory cues sensed by the same primary sensory neuron pair, AWC.[9] We found, under our conditions, Bnz training triggered only an associative learning pathway, while only IsoA training activated a non-associative learning pathway. The initial distinction between the two pathways was functional. This was possible because associative learning could be blocked by the presence of food or serotonin during training since its formation depended on the pairing of the odor with a starvation unconditioned stimulus. Furthermore, these associative and non-associative pathways could be demonstrated to be molecularly distinct with the associative pathway dependent on the PKG *egl-4* and the insulin pathway, while habituation depended on the TRPV channel *osm-9*. These data would be consistent with complete distinction between associative and non-associative learning. However, this simple scenario of each olfactory stimulus triggering a distinct pathway was complicated by the ability of IsoA to also trigger the associative learning pathway, as revealed when tested with a Bnz retrieval stimulus. In addition, we could reveal associative learning after training with Bnz by testing with an IsoA, instead of Bnz, retrieval stimulus (**Fig. 1**). Furthermore, we argued, based on our work and those of other groups, that given the cell autonomous requirement of each of these implicated genes in the AWC, that the majority of information processing and memory processing occurs with the primary sensory neuron itself. This resulted in a scenario in which the two pathways, far from being distinct, are intertwined or "cross-wired" in AWC. In addition, we suggested two genes whose functions traverse the distinction between associative and non-associative learning. In Figure 5b (Pereira and van der Kooy, 2012) we demonstrated that the arrestin homolog *arr-1* functions in the manifestation of both forms of learning to cause a decreased approach to IsoA. In addition, we suggest an explanation for the data from Kuhara et al. (2002) on the hyper-adaptation phenotype of *tax-6* loss of function mutations.[10] This effect may be accounted for by suggesting that loss of *tax-6* function results in artificial activation of the early acquisition phase leading from IsoA sensation, which triggers formation of both forms of learning, thus leading to *a priori* adaptation to both odorants. Consequently, this demonstrates that these forms of associative and non-associative learning and memory are still molecularly integrated, particularly at the early acquisition and at the late retrieval phases. In contrast, the middle phases (late acquisition and early retrieval), those most proximate to the engram, would be most divergent between the two forms of memory. This is consistent with intuitive *a priori* prediction since the associative pathway must evolve mechanisms in which the engram is only formed upon contingent presentation of the CS and US, as well as mechanisms underlying some of its more sophisticated properties (extinction, latent inhibition etc). We argue that the molecular cross-wiring explored in Pereira and van der Kooy is an evolutionary remnant of this process, which we describe as a "bubble" model of pathway divergence (**Fig. 2**). Note that while Moore (2005) proposes that associative learning evolved from habituation through the appearance of sensitization, our model differs in that it does not posit such an intermediate step. Unfortunately, a more complete understanding of this process of divergence necessitates deciphering the identities of

the engrams in both pathways, neither of which is known currently.

The theory outlined above regarding the divergence of the engram relative to the early acquisition and late retrieval phases may appear to contradict that outlined by Gallistel in *The Organization of Learning*.[11] In that work, Gallistel distinguishes between the computational processes required to calculate the magnitude of the memory stored and the mechanism actually utilized in the storage process. He suggests that the former would exhibit extensive diversity based on the myriad of sensory parameters (in vision alone: color, motion, etc.) that could be utilized, in whole or in part, as the conditioned or unconditioned stimulus. The acquisition process would consequently require sophisticated computational operations performed on these parameters in order to generate an output indicating the strength of the association to be stored. Thus evolutionarily, we would expect to see extensive divergence based on the distinct sensory landscape that is experience by each organism in its ecological niche. In contrast, he suggests that the storage mechanism merely has to be able to store the calculated value in a relatively non-volatile form and hence can be generic between vastly different conditioned and unconditioned stimuli. Yet Gallistel's view of the distinction between acquisition or "computation" and storage, in terms of evolutionary divergence, is not incompatible with the view presented here. It is important to note, in our scenario, the divergence of engrams refers to that between the engram for non-associative learning and the novel engram for associative learning early in evolutionary history. Once this distinction has occurred and a genuine mechanism of storing associative memories has emerged, this could serve as a generic device for storing the computed associations between a wide variety of stimuli depending on the organism. Within *C. elegans*, this appears to be the case. For example, the role of insulin signaling (which functions in proximity to the engram) is conserved in associative learning even if the 'computations' required for processing a taste or a smell conditioned stimulus differ.[12,13]

With regard to acquisition, it should also be noted Gallistel was discussing

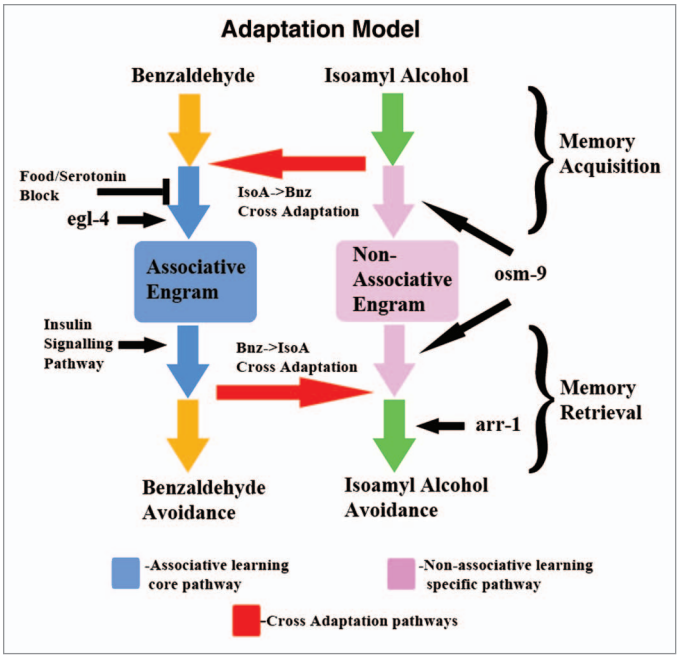

Figure 1. A model for two forms of learning in AWC olfactory plasticity. Originally published as Figure 8 in Pereira and van der Kooy (2012). The model is laid out chronologically from top to bottom, with conditioned stimulus listed at the top and the behavioral responses (avoidance of either odor) listed at the bottom. The black arrows indicate location in the pathway where food/serotonin block or a given gene functions. Each odorant (Bnz or IsoA) begins by triggering a distinct set of processes based on each binding to its cognate chemoreceptor. For Bnz (start top left), this leads to the formation of the associative memory (left box) trace unless blocked by the presence of food/serotonin during food/serotonin sensitive step in the pathway. Furthermore, this process is dependent on EGL-4 function. However, IsoA (start top right) training results in the formation of two memory traces. The non-associative memory (right box) through the adaptation process shown going down or the associative memory through the IsoA→ Bnz unidirectional cross (top horizontal path) and then continuing through the associative learning-specific process that leads to the formation of the associative engram (left box). In this latter case, the pathway from IsoA to the associative memory must similarly go through the food/serotonin-sensitive step and *egl-4*. *osm-9* is only required for the IsoA→ IsoA permutation, while arr-1 has an additional role in Bnz→ IsoA adaptation. This suggests *osm-9* functions upstream, and *arr-1* downstream of the Bnz→ IsoA crossover (bottom horizontal path), although we are unable to determine whether *osm-9* functions before or after the non-associative engram (right box). The ambiguity regarding whether *osm-9* functions in the acquisition or retrieval phase of the non-associative memory is illustrated by the two arrows indicating its possible sites of action in the pathway. Intriguingly, the results for *arr-1* have the implication that associative and non-associative memories may converge on similar molecules, and perhaps mechanism, to mediate the change in behavioral output (decreased attraction to IsoA) seen after learning. The non-associative engram can result in only one possible behavioral output, the adapted response to IsoA when retrieved by that same stimulus (bottom right). In contrast, the associative trace leads to the conditioned response to both odorants by either going down the pathway with retrieval to Bnz (bottom left) or using the unidirectional Bnz→ IsoA cross (bottom horizontal path) for retrieval to IsoA (bottom right). In either case, retrieval of the memory is a process that is insulin dependent. Insulin is depicted with its primary function in retrieval of the associative memory (black arrow), although Lin et al. (2010) suggest it also has a more minor role in associative acquisition, which is here omitted for simplicity.

divergence in the processes for vastly different conditioned stimuli (such as light, tone, or taste) in "higher" organisms, such as rodents. In contrast, here the two conditioned stimuli in question (Bnz or IsoA) are both simple olfactory stimuli, that act on the same neuron pair (AWC).[9] Thus a much smaller degree of difference between the processing of the two stimuli would be expected. Nonetheless, the general principle that early acquisition is conserved in terms of conditioned stimulus, but not memory type, seems to hold. For example, *tax-6* plays a role in the IsoA pathway leading to both associative and non-associative memory formation (The

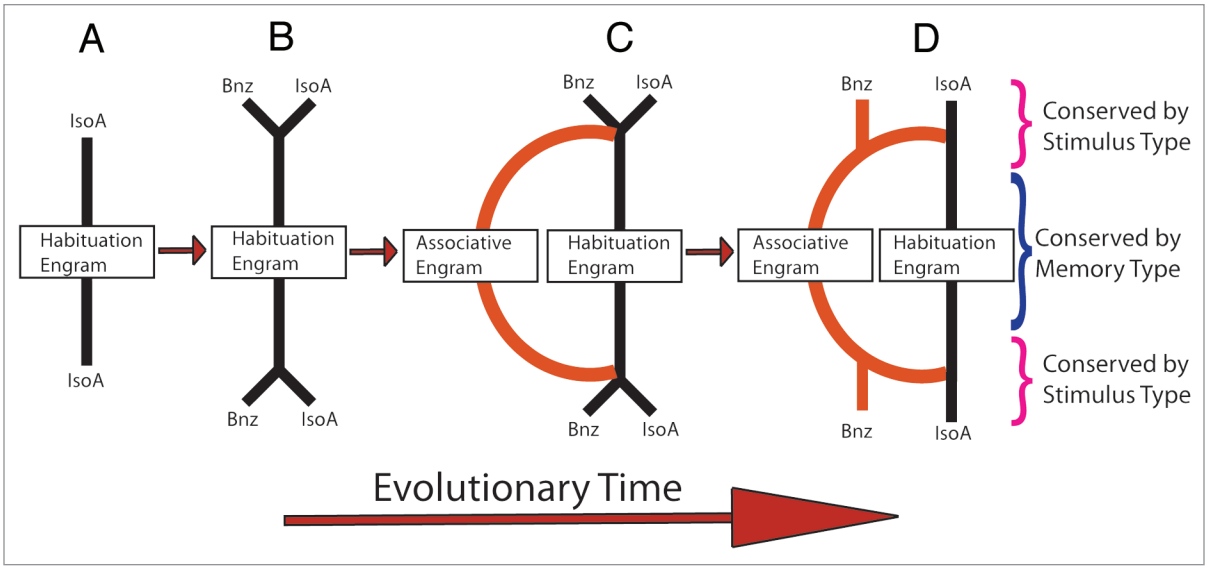

Figure 2. Schematic model of the evolution of associative learning from non-associative learning in *C. elegans* AWC neurons. Evolutionary time is indicated from left to right with each novel adaptation in the pathway demarcated with a red arrow. In all diagrams sensation of the training stimulus is shown at the top, response to the retrieval stimulus is indicated on the bottom and engrams are shown in rectangles. In each diagram follow the pathways (black and orange lines) from top to bottom without backtracking (going up). Each diagram begins at the top with sensation of the training stimulus, move downward toward formation of the engram and then to the response to the retrieval stimulus. (**A**) In the initial stage, AWC senses IsoA, but not Bnz, and can only activate a non-associative habituation pathway. (**B**) Next, AWC gains an ability to sense Bnz through distinct components that also can feed in to the same habituation pathway. This results in 'forking' at the top and bottom of the diagram and in the emergence of reciprocal cross-adaptation. (**C**) A distinct pathway for associative learning (orange) emerges from non-associative learning. This new pathway only results in memory formation when either odorant is paired with an unconditioned stimulus (not shown). Note that in this 'bubble' model, the pathways for the two memory types diverge most at the engram and components proximate to it, while the components of the early acquisition and late retrieval phases are promiscuous between memory type. (**D**) In the last step, Bnz training and retrieval lose their connection to the non-associative pathway through genetic drift or natural selection. Consequently, Bnz training and retrieval now only feed in and out, respectively, of the associative learning pathway. This means that Bnz→ Bnz, IsoA→ Bnz and Bnz→ IsoA paths are now all dependent on associative memory formation while IsoA→ IsoA is still habituative. Note that this change results in a pathway topology identical to that we describe in **Figure 1**. Blue brackets represent the area proximate to the engram that is divergent based on memory type but promiscuous between stimulus (Bnz or IsoA). Pink brackets represent the converse; regions of the pathways in early acquisition and late retrieval that are divergent based on stimulus type but promiscuous between memory types.

same appears to be true in late retrieval with *arr-1* playing a role in both the associative and non-associative response to an IsoA testing stimulus).

The evolutionary model presented in **Figure 2** presumes that benzaldehyde sensation was connected to the non-associative learning pathway prior to the emergence of associative learning (**Fig. 2B**). Yet our data did not reveal the presence of an *osm-9* dependent Bnz adaptation pathway. We propose two possible explanations for this. The first is that this is a purely technical matter given that IsoA has a volatility of 2.37 and Bnz of 0.127 mmHg at 25°C (PubChem). Consequently, the lower level of Bnz exposure from the same volume of odorant employed is not of sufficient threshold to activate the *osm-9* dependent pathway. The second explanation (depicted in **Fig. 2**) suggests that the ability of Bnz to trigger the non-associative pathway existed, but was lost through genetic drift or even negative natural selection. This inevitably leads to the question of why IsoA maintained an ability to activate both pathways, but benzaldehyde did not. An answer requires an appeal to nematode ethology. Previous work in our lab suggested that the strong attraction to Bnz in naïve animals may be a result of conditioning the worms during larval development as Bnz is secreted from the bacterial food source.[14] This must occur through a mechanism distinct from the associative learning pathway explored here since, for example, *ins-1* mutants do not demonstrate impaired naïve Bnz attraction. Evidence for such a benzaldehyde imprinting mechanism comes from Remy and Hobert (2005).[15] However, in certain scenarios benzaldehyde must be predictive of a lack of food, rather than a food source, since our assay depends on pairing the odor with a starvation unconditioned stimulus. Nonetheless, if the informative value of benzaldehyde is only a result of its predictive value with respect to the presence or absence of food, an associative learning pathway would be sufficient to utilize this information and the non-associative pathway can be lost. On the other hand, the informative value of IsoA could be more diverse. It could often be also secreted from bacteria that tend to secret Bnz as well (leading to the logic of both triggering the same food associative learning pathway) or come in large quantities to which an animal would have to habituate to in order to continue efficient foraging, such as fungal colonies.[16] Such speculation will, of course, have to be supplemented with further ecological studies that will improve our understanding of the *C. elegans* niche.

Regardless of which of these two explanations is accurate, the two-input two-output double dissociation strategy employed in our paper is enormously useful for teasing apart these molecular pathways.

Most important, the experiment is easily expandable by simply screening more candidate mutant genes. Yet addition of new genes to the model must be done by careful selection of candidate genes and analysis of their effects. For example, our data suggests *ttx-3* mutation results in impairment in Bnz associative learning but not IsoA habituation (data not shown). However, *ttx-3* was not included in our model because its effect is likely due to a loss of AIY interneuron cell fate specification[17] and AIY has been shown to play a role in Bnz associative learning through an insulin-neuropeptide signaling loop.[13,18] Similarly, *tbx-2* has been reported to eliminate both IsoA and Bnz adaptation.[19] Such a result would, prima facie, falsify our model of two pathways. However, two points should be borne in mind. First, it remains possible that this also is a developmental effect, such that without *tbx-2* an improperly specified AWC lacks the general ability to adapt, though *tbx-2* itself does not participate in the molecular process of olfactory adaptation in either pathway. Second, it should be noted that shared components could function in pathways that are nonetheless distinct. In other words, *tbx-2* could function as an essential part of one complex in associative learning and as an essential part of another in habituation, such that loss of this gene eliminates both. Indeed such a scenario could be a likely result of the divergence process we describe in **Figure 2**. In such a case, it would remain difficult to specifically localize *tbx-2* to a discrete place in our model.

This illustrates the general problem of dealing with mutations that may affect multiple parts of a pathway. We employed Occam's razor and assumed each gene acted at a single point, though in the case of *osm-9* we had two possible locations where *osm-9* might act that were indistinguishable in our data (**Fig. 1**). However, that this may not always be the case was evident from previous work in our lab. In Atkinson-Leadbeater et al. (2004), the authors pioneered the use of the Bnz and IsoA dissociation system we employed.[20] They revealed that when CB4856, an evolutionarily divergent Hawaiian strain, was tested in Bnz→ Bnz it revealed a deficit in conditioning relative to wild type N2. Yet when animals were tested in Bnz→ IsoA, no deficit in conditioning could be seen relative to N2. Most significant, this effect was not an epiphenomenon resulting from polymorphism of the oxygen sensation and group feeding regulator *npr-1* (data not shown). They consequently hypothesized that CB4856 possessed a deficit not in training to Bnz, but specifically in retrieval to Bnz but not IsoA. Nonetheless, this explanation alone is insufficient to explain why IsoA→ Bnz training in CB4856 also was identical to that seen for N2. Consequently, our model requires at least one additional phenotypic difference that strengthens the pathway leading from IsoA to associative memory formation (the IsoA→ Bnz horizontal crossover in **Fig. 1**). In the case of CB4856, it is likely that the multiple functions are due to distinct polymorphisms given the long history of divergence between these two strains and dissociation of these effects will hinge on the identification of the precise polymorphisms acting at each location in the pathway. Nonetheless, it also remains possible that tests of single gene mutations, in isogenic backgrounds, will yield patterns of deficits that require us to posit multiple functions at multiple locations. Such results will serve to increase the depth and complexity of our model, which still remains a humble attempt of one type of nervous system to decipher another.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

This work was supported by the National Science and Engineering Research Council of Canada (grant to D.v.d.K).

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