C. elegans Can Learn To Associate a Temporally Precise Delivery of Paired Stimuli

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Associative learning allows animals to adapt to multiple environmental stimuli that occur proximally in space and time. How molecular and cellular interactions control the formation, maintenance and degradation of learned memories in precise spatiotemporal terms is not fully understood. *C. elegans* can be trained to associate multiple cues and exhibit learned locomotor responses. Short wavelength light is an aversive stimulus that triggers a *C. elegans* escape response (including reversals). We have developed a novel trial-by-trial associative conditioning paradigm for *C. elegans* that utilizes the pairing of a neutral odor stimulus and a noxious light stimulus. After training, worms learned to reverse to the once-neutral smell. This memory is short-term, with memory responses rapidly decreasing over minutes. The transient temporally precise nature of the stimuli delivery has allowed us to demonstrate that timed order and contiguity of stimuli presentation are critically required for the learning, both being features key to associative learning. In a standard classical conditioning paradigm, the odor and light stimuli overlap in time. Notably, worms were even able to learn associations in a trace-conditioning procedure in which the presentations of the light and odor stimuli were separated in time. In humans, trace but not standard classical conditioning is thought to be associated with awareness of the stimulus contingencies. Mutants defective in dopamine, glutamate, and octopamine exhibited defects in learning rates and efficiencies. Intriguingly, mutants defective in serotonin learned more rapidly and more consistently than wild-type worms. How the interplay of order of stimuli and neuromodulation produce an optimal adapted learning process that is sensitive to precision in stimulus timing is incompletely understood. By studying how these factors influence each other at a single-cell level resolution of analysis across a well-defined neural circuit, we hope to gain a detailed understanding of the molecular, cellular and circuit mechanisms that underlie learning processes.