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The foundations of cross-modal plasticity

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ABSTRACT

Cross-modal plasticity is a striking adaptive feature of the brain, whereby the loss of one sensory modality induces cortical reorganization that leads to enhanced sensory performance in remaining modalities. Much is known about the macroscopic modifications in the brain that underly cross-modal plasticity and the associated changes in sensory performance. In contrast there is relatively scant information about the molecular and cellular underpinnings of this mechanism. We hypothesized that cross-modal plasticity is a fundamental feature of the nervous system. As such, it should be found in organisms with brains that are substantially less complex than our own. Indeed, we discovered a cross-modal plasticity mechanism in the roundworm *Caenorhabditis elegans*, whose nervous system is composed of only 302 neurons. Taking advantage of the simplicity of the *C*. elegans nervous system, we were able to comprehensively study cross-modal plasticity from molecule through circuit to behavior.

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In order for any animal to successfully interact with its environment, it must be able to couple its movements and actions with meaningful sensory input. Different species use different combinations of sensory modalities to pick up the most pertinent pieces of information from their particular surroundings. These hard-wired configurations still leave room for flexibility that allows the animal to adjust to changes in the environment, or alternatively, to sustain functionality in the event of possible sensory dysfunction due to disease or injury. One important mechanism that enables this flexibility is cross-modal plasticity.[1-3] Following the loss of input from one sensory modality, plastic changes in the brain lead to altered, often enhanced, performance in remaining modalities. For example, loss of vision may lead to enhanced hearing. Cross-modal plasticity can thus compensate for the missing sensory input by providing more sensory information from other modalities.

A large body of studies has provided valuable information about how cross-modal plasticity is manifested in behavioral change and in associated cortical reorganization.[4-7] So far, these studies have focused on complex mammalian brains. We asked whether cross-modal plasticity exists also in a much simpler nervous system. If so, this would help to redefine the minimal neuronal requirements for cross-modal plasticity, and to facilitate discovery about how cross-modal plasticity is implemented at the molecular, cellular and entire systems level.

We thus considered the nematode *C. elegans*, a microscopic roundworm whose nervous system consists of merely 302 neurons. *C. elegans* dwells in soil and compost, an environment rich in texture and odor. Accordingly, we set to examine whether elimination of the sense of touch to the body, due to a genetic mutation, may affect the sense of smell in this animal. We found that worms that are unable to sense touch become more sensitive to certain attractive odors.[8] This cross-modal interaction depends on the activity of specialized touch neurons that mediate body mechanosensation.[9] Decreases in touch neuron activity due to loss of touch resulted in the strengthening of glutamatergic inhibitory transmission between olfactory sensory neuron AWC and downstream interneuron AIY (Fig. 1A), leading to an enhanced response to smell. We found that this effect can be reversed by either optogenetic stimulation of the

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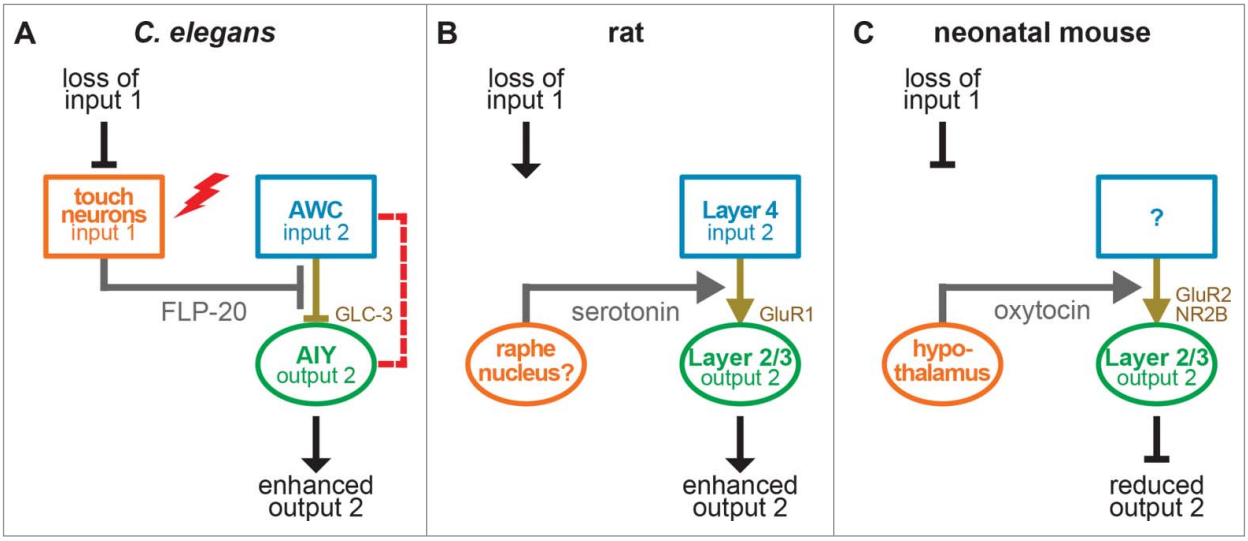

Figure 1. Cellular mechanisms of cross-modal plasticity.[8] (A) In C. elegans loss of mechanosensory input decreases activity in the touch neurons. This in turn reduces FLP-20 neuropeptide signaling from the touch neurons, disinhibiting inhibitory glutamatergic transmission between olfactory neurons AWC and AIY, and enhancing olfaction. The effects of loss of touch input can be bypassed either optogenetically (red lightning symbol), by artificially activating the touch neurons, or through engineering an electrical synapse (red broken line) between AWC and AIY, counteracting the enhanced inhibitory transmission between the two.[8] (B) In rat, loss of visual sensory input results in increased serotonin abundance in the output layer of the somatosensory cortex, strengthening excitatory glutamatergic transmission between layer 4 and layer 2/3 neurons.[11,12] (C) In neonatal mice, visual or somatosensory deprivation reduce hypothalamic secretion of the neuropeptide oxytocin, weakening excitatory glutamatergic transmission to layer 2/3 neurons in somatosensory or visual cortex, respectively, and decreasing their output.[13]

touch neurons (Fig. 1A, red lightning) or by inserting an engineered electrical synapse[10] between AWC and AIY (Fig. 1A, red broken line), which counteracts the enhanced inhibitory transmission between them. We further discovered that the cross-modal signal that links between touch neuron activity and AWC→AIY transmission is a neuropeptide called FLP-20. In normal touch sensing worms FLP-20 is secreted from the touch neurons, suppressing AWC→AIY transmission and dampening olfaction (Fig. 1A). When touch neuron activity decreases due to loss of touch, FLP-20 signaling diminishes, AWC→AIY is no longer suppressed and olfactory acuity increases.

Thus, the C. elegans nervous system, which is substantially less complex than the mammalian nervous system, displays a form of cross-modal plasticity, suggesting that cross-modal plasticity is perhaps a built in fundamental feature of any nervous system. How similar is cross-modal plasticity in *C. elegans* and in the mammalian brain? In mammals cross-modal plasticity appears to have two main forms.[3] (1) Cross-modal recruitment, whereby the deprived sensory cortex is recruited by remaining sensory modalities. (2) Cross-modal compensation, whereby the sensory cortices of the remaining sensory modalities reorganize to improve sensory performance. We have not seen evidence for a possible recruitment of the touch neurons to the olfactory circuit. However, we have clearly demonstrated an adjustment in the olfactory circuit sufficient to enhance olfactory acuity following mechanosensory loss, which is analogous to the mammalian cross-modal compensation mechanism.

Relatively little is known about the molecular and cellular mechanisms that underlie cross-modal compensation in mammals. From what has been revealed several striking similarities appear to exist between mammalian and *C. elegans* cross-modal plasticity. For example, visual deprivation of rats (Fig. 1B, input 1) results in increased serotonin signaling, possibly from the raphe nucleus, which strengthens the excitatory glutamatergic synaptic connections in the barrel cortex between sensory input layer 4 and cortical output layer 2/3, enhancing somatosensory output[11,12] (Fig. 1B, output 2). Conversely, a maladaptive form of cross-modal plasticity has been observed in neonatal mice, whereby visual or somatosensory deprivation (Fig. 1C, input 1) results in reduced secretion of the neuropeptide oxytocin from the hypothalamus, which leads to weakened glutamatergic synaptic transmission to somatosensory or visual cortical output layer 2/3, diminishing circuit output[13] (Fig. 1C, output 2). Thus, cross-modal plasticity both in mammals and in *C. elegans* is (1) implemented by a modulation of glutamatergic synaptic transmission in circuits associated with the remaining sensory modalities, and (2) regulated by long-range modulatory signaling. These two components

are sufficient for cross-modal compensation, as revealed by the optogenetic and synaptic engineering experiments that we performed, which enabled us to manipulate neuronal activity (Fig. 1A, red lightning) and synaptic connectivity (Fig. 1A, red dashed line), respectively, and to thus confirm their causal significance. At the same time, our findings that the source of cross-modal neuropeptide signaling is the deprived sensory circuit itself and that this signaling normally acts to counterbalance and dampen olfaction in wild type worms contribute new insight to our understanding of cross-modal plasticity.

In addition to enhanced olfaction, we identified several other alterations in sensory performance following loss of mechanosensation,[8] suggesting that the *C. elegans* nervous system contains an intricate network of cross-modal signaling mechanisms that adjust the relative weights of different sensory modalities through activity-dependent synaptic modification. Uncovering this network will provide a fundamental understanding about how the nervous system functions as a whole, both normally and following damage.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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