light were adjudged to occur simultaneously in the direction of the time lag experienced during the exposure period. In other words, humans can recalibrate their percept of visual-auditory temporal synchrony, apparently in much the same way they adapt to cross-modal spatial conflicts [5,19].

The results of all of these studies indicate that a dynamic neural mechanism exists for matching the auditory and visual signals arising from a multisensory event. It could be argued that this is rarely needed for coordinating the lip movements and speech sounds of a person within normal conversational range. Nevertheless, when they do occur, changes in physical transmission time and neural processing time appear to be accommodated by shifting the window of integration on the basis of experience or when reliable depth cues are present. This in turn implies flexibility in the capacity of neurons to register the relative timing of multisensory signals and therefore highlights a potentially useful way of probing the adaptive capabilities of the brain.

References

1. Calvert, G.A., Spence, C., and Stein, B.E., eds. (2004). The Handbook of Multisensory Processes. (Cambridge, MA: MIT Press.)
2. Fain, G.L. (2003). Sensory Transduction. (Sunderland, MA: Sinauer Associates.)
3. Dixon, N.F., and Spitz, L. (1980). The detection of auditory visual desynchrony. Perception 9, 719–721.
4. Munhall, K.G., Gribble, P., Sacco, L., and Ward, M. (1996). Temporal constraints on the McGurk effect. Percept. Psychophys. 58, 351–362.
5. Slutsky, D.A., and Recanzone, G.H. (2001). Temporal and spatial dependency of the ventriloquism effect. Neuroreport 12, 7–10.
6. Lewald, J., and Guski, R. (2003). Cross-modal perceptual integration of spatially and temporally disparate auditory and visual stimuli. Brain Res. Cogn. Brain Res. 16, 468–478.
7. King, A.J., and Palmer, A.R. (1985). Integration of visual and auditory information in bimodal neurones in the guinea-pig superior colliculus. Exp. Brain Res. 60, 492–500.
8. Meredith, M.A., Nemitz, J.W., and Stein, B.E. (1987). Determinants of multisensory integration in superior colliculus neurons. I. Temporal factors. J. Neurosci. 7, 3215–3229.
9. Kopinska, A., and Harris, L.R. (2004). Simultaneity constancy. Perception 33, 1049–1060.
10. Engel, G.R., and Dougherty, W.G. (1971). Visual-auditory distance constancy. Nature 234, 308.
11. Stone, J.V., Hunkin, N.M., Porrill, J., Wood, R., Keeler, V., Beanland, M., Port, M., and Porter, N.R. (2001). When is now? Perception of simultaneity. Proc. R. Soc. Lond. B. Biol. Sci. 268, 31–38.
12. Sugita, Y., and Suzuki, Y. (2003). Implicit estimation of sound-arrival time. Nature 421, 911.
13. Lewald, J., and Guski, R. (2004). Auditory-visual temporal integration as a function of distance: no compensation for sound-transmission time in human perception. Neurosci. Lett. 357, 119–122.
14. Alais, D., and Carlile, S. (2005). Synchronizing to real events: subjective audiovisual alignment scales with perceived auditory depth and speed of sound. Proc. Natl. Acad. Sci. USA 102, 2244–2247.
15. Bronkhorst, A.W., and Houtgast, T. (1999). Auditory distance perception in rooms. Nature 397, 517–520.
16. Moore, D.R., and King, A.J. (1999). Auditory perception: The near and far of sound localization. Curr. Biol. 9, R361–R363.
17. Fujisaki, W., Shimojo, S., Kashino, M., and Nishida, S. (2004). Recalibration of audiovisual simultaneity. Nat. Neurosci. 7, 773–778.
18. Vroomen, J., Keetels, M., de Gelder, B., and Bertelson, P. (2004). Recalibration of temporal order perception by exposure to audio-visual asynchrony. Brain Res Cogn Brain Res 22, 32–35.
19. Vroomen, J., and de Gelder, B. (2004). Perceptual effects of cross-modal stimulation: Ventriloquism and the freezing phenomenon. In The Handbook of Multisensory Processes. G.A.Calvert, C. Spence, and B.E. Stein, eds. (Cambridge, MA: MIT Press), pp. 141–150.

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Sensorimotor Integration: Locating Locomotion in Neural Circuits

Neural components of the circuits that transform sensory cues into changes in motor activities are largely unknown. Several recent studies have now functionally mapped the sensorimotor circuits responsible for locomotion behaviors under defined environmental conditions in the nematode *Caenorhabditis elegans*.

Aravinthan D.T. Samuel[1] and Piali Sengupta[2]

Animals are able to navigate diverse and complex environments by transforming sensory cues into patterns of locomotion. The autonomous navigation capabilities of robots are crude in comparison to the highly evolved sensorimotor strategies of living organisms. Bacteria are able to swim up or down chemical gradients using a biased random walk determined by a biochemical system occupying just 1 femtoliter [1]. The nematode is able purposefully to navigate the mechanical, chemical and thermal heterogeneities in its soil habitat using strategies wired into a neural circuit with only 302 neurons [2]. Our technnology is far from matching these remarkable feats of sensorimotor integration. Nevertheless, studying the underlying mechanisms might uncover the solutions that have evolved to address these complex navigational problems, perhaps improving our own design efforts.

Mapping an entire sensorimotor circuit in an animal requires knowledge of the underlying anatomical connectivities of the nervous system, and the ability to manipulate the functions of the component neurons and to define and quantify the behavioral outputs. The nematode *Caenorhabditis elegans* meets all these requirements with the additional benefits of physiology and powerful genetics. But having a 'wiring diagram' — an anatomical description of the connectivities of all neurons — is not enough. Neurons are highly interconnected: practically every neuron has multiple synaptic inputs and outputs, an intricate Gordian knot of synaptic connectivity [2]. Only a few previous studies [3–5] have attempted to ascribe functions to these connections. In three studies [6–8] of the sensorimotor correlates of worm locomotion, we are beginning to see the knot unravel.

Worm locomotion lends itself to quantitative description as it can

Local search, <15 min off food

Omega turn

Start   End

ASI — AWC   ASK

AIY   AIB

*Command interneurons
for reorientation*

Long-range roaming, >15 min off food

End

Start

ASI — AWC   ASK

AIY   AIB

*Command interneurons
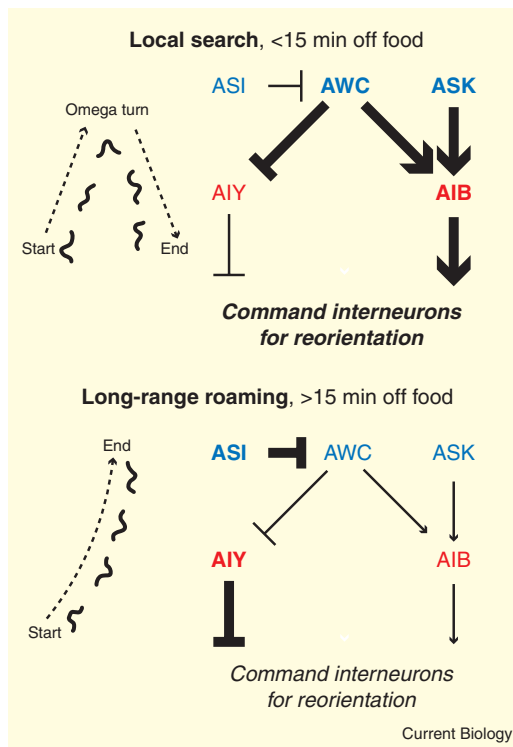for reorientation*

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Figure 1. Major neuronal components of the sensorimotor circuits in *C. elegans* that mediate local search and long-range roaming behaviors.

A sequence of images showing a typical reorientation event including an omega turn (top left) and persistent forward movement (bottom left) are shown. Major sensory neurons (blue) and interneurons (red) implicated in the local search and roaming behaviors are indicated. Arrowheads indicate proposed excitatory connections; T-bars indicate proposed inhibitory connections. Implied functional connections are shown; connections are not necessarily direct.

be described as alternating sequences of forward movements, reversals and turns. Worms switch between forward and backward movements as a function of the activities of a circuit that acts as a bistable switch [3,9,10]. This circuit consists of the forward and backward command interneurons which synapse onto motorneurons. Gray *et al*. [6] further dissected the backward movement into three categories: short reversals, which are accompanied by small changes in trajectory; long reversals; and omega turns, which result in ~180 degree changes in direction.

Modulating the rates and frequencies of each of these behavioral components enables the worm to undergo net forward or backward movement, and to alter its direction of movement in response to specific environmental conditions. The neuronal circuits that feed sensory cues into the command interneuron layer to effect these behaviors were until recently largely unknown. A major contribution of the three recent studies [6–8] has been to extend the circuits for worm locomotion *upstream* through the layers of

interneurons and sensory neurons that integrate sensory cues to regulate these behavioral decisions (Figure 1).

Worms have different patterns of motility when crawling in the presence or absence of bacterial food [5–8,11]. Upon removal from food, worms immediately probe the local vicinity in multiple directions, with bursts of forward movement, frequent long reversals and turns, and suppressed short reversals. Similar patterns of movement have been described in other organisms, and this is referrred to as area-restricted search behavior [12]. But if food is still not found after about 12 minutes, worms switch to long-range roaming, suppressing all types of reorientation and crawling long distances with persistent forward movements. These exploratory movement patterns are distinct from the directed movement towards specific chemical or thermal cues (cues presumably connected with the presence of food), but the new studies [6–8] indicate that the neural networks for exploratory and taxis behaviors are partly overlapping.

To identify the relative contribution of each of the

synaptic connections from the sensory neuron to the command interneuron layer to a particular behavior, the investigators [6–8] systematically ablated neurons, singly and in combinations, and quantified the effects on navigation behaviors. The details of the behavioral assays used, the neurons tested, and the measurements performed differ in each study, but details aside, a functional map for worm locomotion emerges along with several surprises.

One surprise is that disrupting all chemosensory neurons did not affect patterns of locomotion in the presence of food, but did affect behavior when worms were taken off food. Indeed, previous work has suggested that movement in the presence of food might be regulated primarily by mechanosensory inputs [11]. Removal of the AWC or ASK chemosensory neurons, for example, resulted in decreased long reversals and/or omega turns that drive the local search — also called 'pivoting' — behavior immediately upon removal from food. As suggested by Wakabayashi *et al*. [8], AWC and ASK might be silent in the presence of food and active in its absence, resembling the OFF-center neurons in the vertebrate retina. Adaptation to the absence of food might explain the transition from local searching to the long-range exploratory phase.

Gray *et al*. [6] found that ablation of the AIB interneurons gave similar effects, suggesting a functional connection between AWC, ASK, and AIB. In contrast, removal of the ASI or AIY interneurons resulted in increased long and short reversals, hinting at an opposite or antagonistic pathway. AIY is the postsynaptic partner of AWC, but AWC and AIY have opposite effects on the observed behaviors, suggesting that at least under the experimental conditions examined, AWC may have inhibitory connections to AIY. It is possible that several additional synaptic connections may also be inhibitory. Gray *et al*. [6] also found sophistication at the level of motor control of specific

reorientation patterns, with distinct neuronal correlates for short and long reversals and turns. These results were not predicted from the wiring diagram, but emerged from the detailed functional analyses of movement described in these studies.

It is possible to interpret these results as showing a hierarchical layering in the circuit diagram for locomotion, similar to robots using reactive navigation paradigms. One can propose that the behavior on food is the lowest layer and is expressed in the absence of sensory inputs. At the next layer up, the ASI sensory and AIY interneurons decrease reversal frequency in the absence of food. This reversal-suppressing activity is further modulated by inputs from the AWC and ASK (and other) sensory neurons immediately on removal from food to increase reversal frequency. In this simple mechanism, the same neuronal components may be employed in multiple behavioral contexts, depending on the identities and functions of additional neurons incorporated into the circuit.

What next? Visualizing the activities of the component neurons during the different navigation behaviors would provide crucial information regarding their activity states. It would also be useful to identify the genes and signaling pathways that mediate these behaviors and determine what allows a switch from one behavioral state to another. Dopamine signaling has been shown to regulate the transition from local search to exploratory behavior [5]; what are the neurotransmitters that modulate these transitions under specific environmental conditions? Better and more quantitative ways of analyzing all aspects of worm locomotion are essential (see for example [13]). Functional mapping of the locomotor circuits in *C. elegans* is a first step towards understanding how animals utilize their nervous systems to make decisions and to generate complex behaviors.

References
1. Berg, H.C., and Brown, D.A. (1972). Chemotaxis in *E. coli* analysed by three-dimensional tracking. Nature *239*, 500–504.
2. White, J.G., Southgate, E., Thomson, J.N., and Brenner, S. (1986). The structure of the nervous system of the nematode *Caenorhabditis elegans.* Phil. Transact. R. Soc. Lond. B. *314*, 1–340.
3. Chalfie, M., White, J.G., Southgate, E., Thomson, J.N., and Brenner, S. (1985). The neural circuit for touch sensitivity in *Caenorhabditis elegans.* J. Neurosci. *5*, 956–964.
4. Mori, I., and Ohshima, Y. (1995). Neural regulation of thermotaxis in *Caenorhabditis elegans.* Nature *376*, 344–348.
5. Hills, T., Brockie, P.J., and Maricq, A.V. (2004). Dopamine and glutamate control area-restricted search behavior in *Caenorhabditis elegans.* J. Neurosci. *24*, 1217–1225.
6. Gray, J.M., Hill, J.J., and Bargmann, C.I. (2005). A circuit for navigation in *Caenorhabditis elegans.* Proc. Natl. Acad. Sci. USA *102*, 3184–3191.
7. Tsalik, E.L., and Hobert, O. (2003). Functional mapping of neurons that control locomotory behavior in *Caenorhabditis elegans.* J. Neurobiol. *56*, 178–197.
8. Wakabayashi, T., Kitagawa, I., and Shingai, R. (2004). Neurons regulating the duration of forward locomotion in *Caenorhabditis elegans.* Neurosci. Res. *50*, 103–111.
9. Zheng, Y., Brockie, P.J., Mellem, J.E., Madsen, D.M., and Maricq, A.V. (1999). Neuronal control of locomotion in *C. elegans* is modified by a dominant mutation in the GLR-1 ionotropic glutamate receptor. Neuron *24*, 347–361.
10. Brockie, P.J., Mellem, J.E., Hills, T., Madsen, D.M., and Maricq, A.V. (2001). The *C. elegans* glutamate receptor subunit NMR-1 is required for slow NMDA-activated currents that regulate reversal frequency during locomotion. Neuron *31*, 617–630.
11. Sawin, E.R., Ranganathan, R., and Horvitz, H.R. (2000). *C. elegans* locomotory rate is modulated by the environment through a dopaminergic pathway and by experience through a serotonergic pathway. Neuron *26*, 619–631.
12. Kareiva, P., and Odell, G. (1987). Swarms of predators exhibit 'preytaxis' if individual predators use area-restricted search. Am. Naturalist. *130*, 233–270.
13. Feng, Z., Cronin, C.J., Wittig, J.H., Sternberg, P.W., and Schafer, W.R. (2004). An imaging system for standardized quantitative analysis of *C. elegans* behavior. BMC Bioinformatics *5*, 115.

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Brain Asymmetry: Switching from Left to Right

The relationship between structural and functional asymmetries in the brain remains unclear. A recent report describes a zebrafish mutant that provides us with some enticing clues about this relationship.

Shin-Yi Lin and Rebecca D. Burdine

The vertebrate brain contains a number of striking left–right asymmetries [1,2]. For example, in humans language is processed predominantly in the left hemisphere — an observation that has become a classic example of brain lateralization [2]. However, some individuals have been found who process language with either their right or both hemispheres, and they have language skills similar to those with typical left-sided processing [3].

It is not clear, therefore, to what degree lateralized processing influences our language abilities. We also do not understand how this and other functional asymmetries are initiated or maintained in the brain during development. One possibility is that asymmetries in the structure of the brain may influence the subsequent function of the organ. Yet individuals with anatomical reversals in brain structure, due to a condition called *situs inversus totalis*, still retain left-sided language processing [4].

These results suggest that, for some cognitive tasks, function may not follow structure. Experiments reported in this issue of *Current Biology* [5] challenge us to re-examine the relationship between structural and functional asymmetries in the brain, and prompt further investigation of the connection between left–right patterning in the brain and the rest of the body.