Imaging the Neural Basis of Locomotion

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To investigate the fundamental question of how nervous systems encode, organize, and sequence behaviors, Kato et al. imaged neural activity with cellular resolution across the brain of the worm Caenorhabditis elegans. Locomotion behavior seems to be continuously represented by cyclical patterns of distributed neural activity that are present even in immobilized animals.

The worm Caenorhabditis elegans might seem simple, but there’s a lot going on both inside and out. It explores the world with a series of sinusoidal swims punctuated by pirouettes—quick reversals or sharp turns. Poking the animal reliably evokes a reflexive reversal (de Bono and Maricq, 2005). Other stimuli, like chemicals, can elicit more stochastic changes, for example, when they suggest the presence of food. When worms detect decreases in the amount of food nearby, the probability they will pirouette increases (de Bono and Maricq, 2005). This behavior program helps worms navigate toward areas with high food concentration in a non-deterministic manner that’s difficult for predators to exploit. How does C. elegans produce variable behavior sequences? How does it integrate diverse sensory information to adjust the probabilities of its behaviors? Understanding how a nervous system encodes, organizes, and sequences behaviors is a central problem in systems neuroscience—whether in worms or humans. In this issue of Cell, Kato et al. (2015) shed new light on how neural dynamics in the worm produce behavior. By combining several new technologies, including near-whole-brain imaging of neural activity at single-cell resolution, Kato et al. (2015) provide evidence that motor commands in C. elegans are represented across large populations of neurons with cyclical dynamics, building on and extending related observations across a variety of behaviors such as digestion (Marder and Calabrese, 1996) and decision-making and across organisms ranging from leeches (Briggman et al., 2005) to primates (Churchland et al., 2012).

Kato et al. (2015) imaged neural activity across ~100 neurons in the brains of worms held immobile in a small channel. They used GCAMP, a genetically encoded calcium indicator that elicits green fluorescence in active neurons, and a fast, commercially available, confocal microscope to capture volumetric images of the entire brain every third of a second. More sophisticated microscopes have been used to image neural activity in larger volumes at higher speeds (Prevedel et al., 2014), but Kato et al. (2015)’s system achieved single-neuron resolution across most of the brain and, when combined with the extensive existing knowledge of C. elegans neural anatomy, supported identification of most neurons. Despite being held immobile, the worms’ brains fluttered with activity over long durations (~20 min per worm). The resulting data—100-dimensional time series describing neural activity, one dimension for each cell—are difficult to understand with the naked eye and require higher-level analysis. Kato et al. (2015) employed principal component analysis (PCA) to reduce the high-dimensional data to two- or three-dimensional trajectories (Figure 1A). These dynamical portraits captured the structure of a neuronal population in a simpler and more interpretable form, revealing trajectories of neuronal activity that followed a cyclical, highly repeatable pattern. That is, one stereotyped pattern of neural activity is followed by a second stereotyped pattern and so on, until the original pattern occurs again and the cycle repeats. In addition, Kato et al. (2015) observed that the activity of many neurons contributed to this neural representation, suggesting that these neural dynamics, though restricted to just a couple of dimensions, were distributed across a large number of neurons. Cyclical neural dynamics have been observed in the generation of rhythmic motor behaviors like digestion and swimming (Marder and Calabrese, 1996), as well as non-periodic behaviors like reaching for a target (Churchland et al., 2012). Low-dimensional, distributed neural representations also have been observed in many systems, including locomotion behavior choice (Briggman et al., 2005) and odor-identity encoding (Stopfer et al., 2003). Both oscillatory and distributed neural representations are hypothesized to be fundamental neural organizational strategies (Briggman and Kristan, 2008), about which numerous open questions remain. How does neural activity state relate to behavior? How are cyclical patterns generated and how do the many neurons in this network coordinate their activity? What are the advantages of these implementations? How are sensory information, learning, and the animal’s history integrated to change the neural representation?

Through a combination of analysis and experiment—many exploiting the unique experimental capabilities in C. elegans—Kato et al. (2015) tried to demystify these neural trajectories with more concrete observations. They performed a second set of experiments in which they imaged neural activity in freely behaving worms to observe locomotion concomitant with neural activity. In these more limited recordings, they used genetic techniques to target calcium indicator expression to cells identified as important by the PCA analysis of whole-brain data. Surprisingly, clusters of the neural trajectory space, defined solely on the basis of neural activity, corresponded to different locomotion behaviors: swimming forward, reversing,
and ventral and dorsal turns (Figure 1B). Thus, it appears that a large portion of the C. elegans neural activity, even in immobilized animals, encodes the (fictive) locomotor state. The neural activity flow (Figure 1B) has similarities to a continuous version of a behavior state transition diagram (Figure 1C), a representation often used to visualize the types and probabilities of behavior transitions observed (Anderson and Perona, 2014).

A surprising feature of these patterns of neural activity is that they are largely self-generated. Eliminating activity in an output motor command neuron left much of the cyclical activity patterns intact, and environmental input also seemed to have limited influence on the shape of the neural activity manifold. Instead, increasing oxygen concentration increased the frequency with which activity entered regions of neural space associated with reversals. Taken together, these observations suggest that a large fraction of the brain of the worm is constantly oscillating between states which, when the animal is freely behaving, cause it to perform different locomotion behaviors. In this framework, sensory information modulates the probabilities of entering and leaving these states. Thus, these neural dynamics may explain the variability exhibited in the worm’s locomotion behavior (Gordus et al., 2015).

Kato et al. (2015) have opened up whole-brain imaging in C. elegans as a new, powerful system for investigating how the brain sequences behavior, as well as how cyclical and distributed neural representations are generated and maintained. Although behaviorally simpler than animals like flies, mice, or primates, C. elegans has experimental advantages, many demonstrated here: transparency, developmental stereotypy, thoroughly characterized anatomy, and genetic control. In future research, this system might be enhanced if whole-brain imaging were possible in freely behaving animals, making the neural-behavioral relationships explored here more direct. It would also be aided by development of faster indicators of neural activity, other fluorescent sensors, and microscopes with subcellular resolution. New analytical methods for relating neural trajectories to behavior might also result in new discoveries and will become increasingly necessary as these techniques are extended to more complex animals like zebrafish, fruit flies, mice, and, eventually, primates and humans.

REFERENCES