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Running to stand still

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A modified two-photon microscope images neural activity in mice that are running on a treadmill.

When was the last time you exercised, drove a car or did your taxes while you were asleep? Most stimulus-induced neural activity occurs during waking hours; however, most neural imaging techniques require animals to be anesthetized. Now Dombeck *et al*. report two-photon microscopy in awake, behaving mice in a recent article in *Neuron*.

Relative to wide-field imaging with camera-mounted microscopes, two-photon microscopy offers increased resolution and tissue penetration. The authors reasoned that if the subject's head remained immobilized, voluntary body movements should not disturb high-resolution two-photon imaging. They designed a treadmill that mice could use while tethered to a two-photon microscope stage.

The authors inserted a cranial window fused to metal plates into mouse skulls and fastened the plates to the microscope stage. With their heads immobilized underneath the stage, mice ran forward, backward and sideways on a styrofoam ball supported by pressurized air. The authors recorded the direction and speed of the ball's motion with two optical computer mice.

By imaging mice expressing yellow fluorescent protein under the control of the neuronal *Thy1* promoter, the authors estimated that mice moved their heads on average 2-5 μm during running bouts. They corrected for these movements with a Hidden Markov Model, which calculates the probability of a position change in the x-y coordinate plane. They focused up and down to correct for movements in the vertical plane.

Does neuronal activity correlate with running behavior? The authors loaded neurons and astrocytes in the hindlimb sensory cortex with a calcium imaging dye. They puffed air on the contralateral hindleg to initiate running and imaged neural activity from defined neurons and glia, subtracting out activity that was caused by head movement. All of the mice showed running-induced neural activity (calcium transients). On average, 77% of neurons showed at least 1 activity-induced calcium transient per minute. In approximately 16% of neurons, 11% of astrocytes and 53% of the neuropil, calcium transients strongly correlated with running bouts, suggesting that running correlates most with activity in neural processes. Although in neurons, calcium transients occurred in phase with running bouts, in many astrocytes, calcium transients lagged one second behind the onset of running activity.

The authors plan to add biologically relevant visual, auditory and olfactory stimuli with video screens, speakers and air tubes

mounted near the stage. These 'virtual reality' stimuli should allow researchers to observe the activity of neural networks important in navigating the mouse environment.

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1. Dombeck, D. A., Khabbaz, A. N., Collman, F., Adelman, T. L. & Tank, D. W. Imaging large-scale neural activity with cellular resolution in awake, mobile mice. *Neuron* **56**, 43–57 (2007). | Article | PubMed |

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