To understand human brain imaging, Stanford scientists look to flies

By Grace Huckins

To try to figure out how the human brain works, cognitive neuroscientists depend heavily on the presumed relationship between energy consumption and neural activity. Functional magnetic resonance imaging (fMRI) is their most essential tool, and they use it to observe how activity in brain regions ebbs and flows. But fMRI can't actually measure the electrical firing of individual neurons—instead, it watches for increases and decreases in the flow of blood across the brain.

Neurons consume energy when they fire; and to produce usable energy in the form of ATP, cells need oxygen; and blood is what carries oxygen throughout the body. It isn't difficult to imagine, therefore, that the brain regions with the most blood flow might also be the most active, and results from across neuroscience have supported the validity of this approach. fMRI measurements are closely correlated with the local field potential, an electrical signal that reflects the activity of small populations of neurons. And by studying slices of the brain under a microscope, researchers have been able to observe a tight relationship between cell firing and the production of ATP. But the link between energy metabolism and neuronal activity had not been directly observed at fast timescales in a living animal. To bridge that gap, a group of neurobiologists at Stanford University - Kevin Mann, Stephane Deny, Prof. Surya Ganguli, and Prof. Tom Clandinin - decided to look at flies.

Flies may seem a bizarre place to search for clues about the workings of a technology used to study humans. But Clandinin says that metabolism is such an evolutionarily ancient process that information about fly brain metabolism—on the cellular level, at least—is relevant to the human brain. "How neural activity might be correlated with glucose metabolism and energy production—that's all stuff that's evolutionarily common between flies and humans," he says.

And flies have some enormous advantages as experimental animals. They are tiny, reproduce quickly, and have relatively well-understood brains—and they are easy to genetically manipulate. To examine metabolism and neuronal activity at the same time, the researchers engineered their flies to produce two proteins that, by emitting different amounts of light, indicated changes in neuronal firing or ATP levels. So just looking at the fly brains was enough to determine how neuronal activity affected ATP levels. Using this technique, the researchers found that neuron firing and ATP levels were indeed correlated, and the results of their experiments were published in *Nature* last year.


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That correlation is in and of itself good news for researchers who depend on fMRI. But the researchers also tested the assumptions of fMRI more directly. A very common strategy for analyzing fMRI data involves constructing a “functional connectivity matrix,” which quantifies how similar signals in different pairs of brain regions are to each other. The team built such a matrix first from their neuronal activity data, and then from their ATP metabolism data, and found that the matrices inferred from the two types of data were very similar to each other. When fMRI researchers construct functional connectivity matrices from blood flow data, therefore, those matrices are likely similar to the matrices they would observe if they had access to brain activity data.

There was a curious quirk in the data, however—while slow fluctuations in ATP and neuron activity, on the order of tens of seconds, were strongly correlated with each other, fast changes, on the order of a second, were not, suggesting ATP levels were insensitive to fast changes in neuronal activity. To probe this observation further, the researchers embarked on a new experiment where they stimulated individual neurons and then watched for changes in neuronal activity or ATP levels. As predicted, neuronal activity increased after stimulation. But so did ATP.

This was puzzling—if firing consumes energy, shouldn’t active neurons show *lower* levels of ATP? One likely explanation is that neuronal activity does deplete ATP, but that depletion is offset by an increase in ATP production sparked by that same activity. And supercharging ATP production after firing could be a sensible strategy for neurons. A cell that is active might reasonably continue to be active—if a cell that is sensitive to the appearance of a particular object, for example, fires, it may keep firing as long as the object doesn't disappear. The authors hypothesized that, by producing extra ATP, neurons prepare themselves to continue firing once they've started. The ATP surge, the team observed, can last for hundreds of seconds, which supports the idea that its purpose is to equip the cell for future activity.

Interestingly, this idea matches up well with theories about how fMRI works—active brain regions demand oxygen and so increased blood flow provides that oxygen, just like active neurons need ATP and so ratchet up metabolism to provide themselves with that ATP. Though these cellular processes might seem tiny, compared to the scale of the human brain, Clandinin says they might actually have implications for neuroimaging. Engineers are constantly working to improve the resolution of fMRI, in order to enable it to detect ever-faster and ever-more-localized changes in blood flow. But because fMRI measures brain activity via metabolism, the speed of fMRI might be intrinsically limited. Firing is fast—but, as this study demonstrated, activity-related changes in metabolism are slow. There's little point, therefore, to making observations on a timescale shorter than those changes. "The measurements that we've made argue that there's a ceiling to that beyond which you shouldn't bother," Clandinin says.

Clandinin is also interested in the implications of this study beyond fMRI. There's still a great deal to learn, he says, about the relationship between neuronal firing and energy metabolism in the fly brain. Brains consume enormous amounts of energy, so neuroscientists are constantly theorizing about how the brain might process information in an energy-efficient way. Clandinin thinks this fly system might provide a great opportunity to study how exactly that tradeoff manifests, on a molecular level. "Flies are a great model for that because they clearly operate under kind of an extreme metabolic constraint," he says. They are small and lightweight; they don't carry the energy stores that humans do. Somehow, Clandinin speculates, the big, slow surges in ATP provoked by neuronal activity have something to do with managing energy stores—with permitting a tiny, near-weightless creature to nevertheless navigate the world, find food, reproduce, and survive.

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