

Emotions in the brain

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David Anderson, Seymour Benzer Professor of Biology

This year has been a busy one for biologist David Anderson, Caltech's Seymour Benzer Professor of Biology. In 2014 alone, Anderson's lab has reported finding neurons in the male fly brain that promote fighting and,



in the mouse brain, <u>identified a "seesaw" circuit that controls the transition between social and asocial behaviors</u>, <u>neurons that control aggressive behavior</u>, <u>a neural circuit that controls anxiety</u>, and <u>a network of cells that switches appetite on and off.</u>

The flurry of discoveries, made possible using state-of-the-art neurobiology techniques such as optogenetics (a technique that uses light to control neural activity), is the result of years of research by the lab to understand emotions and how they are encoded in the brain. We recently spoke to Anderson about this work, his goals, and how the interdisciplinary collaborations he is building at Caltech are helping to spur a revolution in neuroscience.

How would you define an "emotion"?

There has been ongoing debate for decades about what "emotion" means, and there is no generally accepted definition. In an article that Ralph Adolphs [Bren Professor of Psychology and Neuroscience and Professor of Biology] and I recently wrote, we put forth the view that emotions are a type of internal brain state with certain general properties that can exist independently of subjective, conscious experience. That means we can study such brain states in animal models like flies or mice without worrying about whether they are consciously aware or not. We use the behaviors that express those states as a readout. For example, behaviors that express the emotion state we call "fear" are freezing and flight. Behaviors that express "anger" include various forms of aggression.

So you study these behaviors to get at the underlying emotion and its neural circuitry?

Ultimately, yes. We use genetically based techniques that have been



developed over the last 10 years or so—including but not limited to optogenetics, imaging of brain activity, and mapping of neuronal connections—to try to identify specific populations of neurons in the brain that control these "emotional" behaviors. Are there specific populations of neurons in the brain that control aggression, for example? If so, where are those neurons located in the brain? How do they function? Do they only control behaviors, or do they encode internal states as well?

Do you know any of these answers yet?

We have identified, in fruit flies and in mice, small populations of neurons that control aggression. In flies, we have identified a population of as few as three to five neurons that, when activated, are sufficient to make a fly fight.

In the mouse, we have identified an analogous population in a deep brain structure called the hypothalamus. There are about 2,000 of those neurons. Activating these neurons is sufficient to promote aggression, and inhibiting these neurons can stop a fight dead in it tracks.

Do you think similar populations of "aggression" neurons are found in humans? Could they be related to problems with violence in people?

We're studying these problems because they are fundamental to understanding how the brain works, but certainly it doesn't escape our attention that violence is a pervasive public health problem. My feeling is that we need to understand the basic brain circuitry that controls aggression if we are ever going to understand abnormal forms of aggression, such as sexual violence.



In that respect, it's interesting that we have discovered, in both flies and mice, small populations of neurons that control both aggression and mating (reproductive) <u>behavior</u>. So in a male mouse, for example, if you optogenetically stimulate these neurons at a lower light intensity, the animal will try to mate instead of fight. At a higher stimulation intensity, the animal switches from mounting to attack. It's amazing to watch.

A really important objective over the next several years is to try to figure out how the brain can keep sex and violence separated if the neurons are so intimately related to each other, starting with the question of whether they are the same or different neurons. Obviously that could have implications for sexual violence, for example. It could be that there are people who, as it were, have their wires crossed in these regions of the brain, and that causes them to express violent behavior inappropriately.

With regard to your recent study that identified neurons that function as a "brake" on appetite, could that same kind of mis-wiring contribute to eating disorders?

It could. I think the field as a whole—meaning the field of psychiatry—is moving away from the popular idea that psychiatric disorders are due to chemical imbalances in the brain, as if the brain were a bag of soup flavored with dopamine and serotonin, to the idea that psychiatric disorders are due to dysfunctions of brain circuitry as well as chemistry.

You've found a "seesaw circuit" in the amygdala that tips between social behavior and self-directed behavior depending on which of two populations of neurons is active. Did you expect the brain to be wired



this way?

No. It was also completely unexpected that these two populations segregate according to the most basic distinction between neurons in the brain: inhibitory neurons and excitatory neurons. Inhibitory neurons control the social behaviors. Excitatory neurons control the self-grooming behaviors. It did not have to be that way.

Could the proportion of these neurons explain something like personality—whether a person is introverted or extroverted?

That is a fascinating question—whether differences in the behavior of individuals might reflect differences in the relative numbers of different types of neurons. We're trying to see if that is true in different strains of laboratory mice that show different levels of aggression. It is a new direction of research in my lab.

Does the discovery of these kinds of circuits suggest possible treatments for human disorders? Could you alter a circuit to change behavior?

It might be possible that, if you found the right population of neurons, you could override the effect of a gene mutation to promote autism or some other psychiatric disorder by pushing the activity of the circuits in a different direction.

Tip the balance of the seesaw . . .

Tip the balance of the seesaw in the other direction. However, this is very far in the future.



But to take a step back to the 35,000-foot level: All of this is happening in the context of a field-wide revolution in neuroscience, a revolution in technology for understanding the brain at the neural circuit level. When I was on the advisory committee for the Obama BRAIN project, we decided that it should focus on supporting the development of this kind of technology.

The technology—in optics and nanotechnology and molecular biology and genetics—allows us to identify populations of <u>neurons</u> that control behaviors, map their connections, measure their activity during behaviors, and manipulate their function, turning them on and off, with a laser-like precision that we could never do before.

If you think of specific populations as a needle in a haystack, these technologies allow us to see and touch and manipulate the needle separately from the haystack. That doesn't mean it won't affect the haystack, but at least we know what we're doing.

Your lab's focus changed as a result of the advent of these new methods. Can you tell us about that?

Around the early 2000s, I decided that this area of neuroscience was going to be ripe for new discoveries, although much of this new technology didn't exist then. Caltech helped me to completely retool my laboratory, to move from the study of brain development and stem cell biology to the study of neural circuits and behavior—a major transition from both the intellectual and technical standpoint. It was sort of like turning a sailboat into a motorboat without stopping moving.

Do you have a vision of how the field will develop in the future?



This work is increasingly interdisciplinary. It needs molecular biology. It needs optical physics. It needs nanotechnology. It needs modeling, theory, computer science, and electrical engineering. No one laboratory can be competent in all of these different areas.

What has kept me here at Caltech is the ability to collaborate with people from different disciplinary backgrounds. What I am excited about, going forward, is to try to develop a new style of research here in which several laboratories devote their collective energies toward solving a challenging problem in a collaborative way, that they couldn't do if they just stayed in their silos and did their own thing.

Have you already set up some of these kinds of collaborations?

Yes. For example, I've been working since 2009 with Pietro Perona [Allen E. Puckett Professor of Electrical Engineering], who has applied his skills in machine vision and machine learning to figure out how to automatically measure aggressive behaviors in flies. We are trying to develop similar technology for the mouse as well. It is not only enormously labor-saving but opens a new, more quantitative approach to describing behavior. And there is also my collaboration on emotion theory with Ralph Adolphs in the Division of Humanities and Social Sciences.

One of the strong recommendations of the BRAIN committee was to promote these kinds of interdisciplinary, cross-laboratory projects. I think it is important for Caltech to recognize that because of its strength in computer science, applied physics and engineering, and its strength in neuroscience, psychology and social sciences, it is ideally poised to promote and facilitate collaborations between physical scientists and neuroscientists.



Interdisciplinary work is something that Caltech does very well.

It is. But in this area of interdisciplinary neuroscience, we have particularly exciting opportunities to engage faculty in multiple divisions across campus. I think this is an ideal moment for us to seize the opportunities identified by the BRAIN initiative, and take advantage of what we do best.

When you say "what we do best," what do you mean?

Nimble, interdisciplinary and creative collaborations between labs, which would be harder to implement at larger institutions. Caltech is perfectly positioned to exploit the revolution in neuroscience, in its own unique and interdisciplinary way—exploiting our growing strength in neuroscience and our traditional strengths in genetics, the physical sciences, and engineering—to solve the enormous challenge of how the brain works.

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