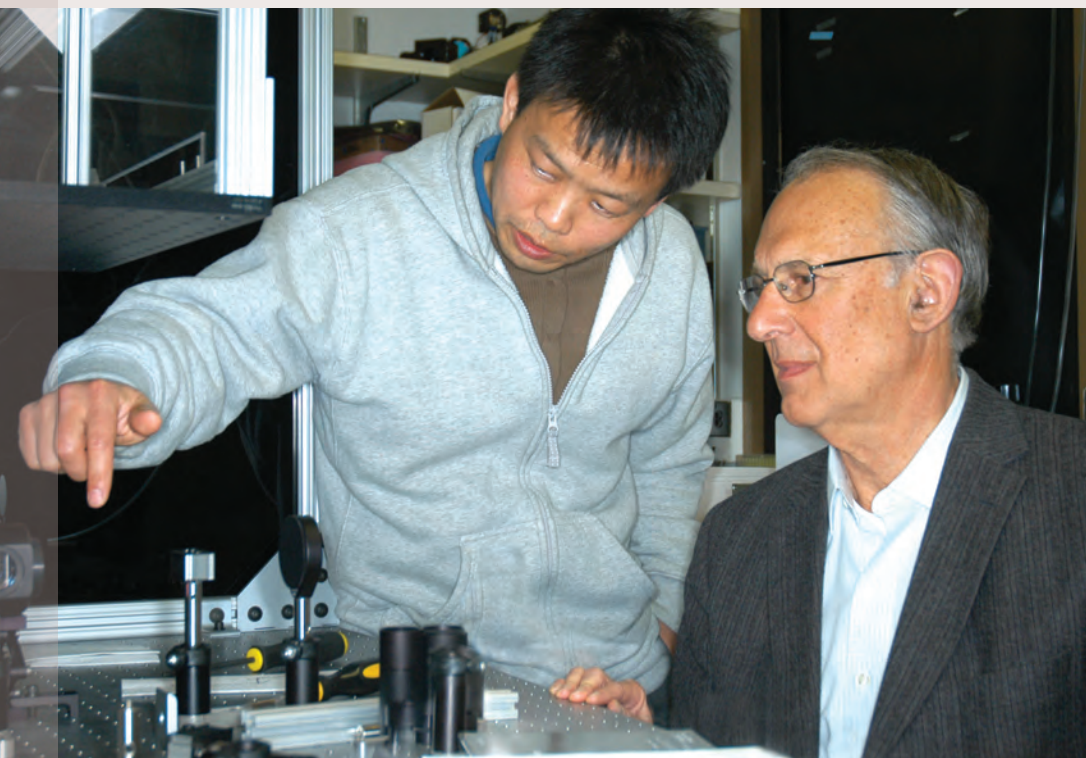


# On depression's trail



Bo Li and Fritz Henn are studying depression's neural circuitry

More than 20 million Americans will leave their doctors' offices this year with prescriptions for antidepressant drugs, dozens of which now line pharmacy shelves. No one knows precisely how these drugs combat depression's symptoms. Why they and other modes of therapy often fail is also unknown, sending neuroscientists in search of depression's neural circuitry within the brain and ideas for better, safer treatments.

At CSHL, Professor Fritz Henn and Associate Professor Bo Li are focusing on a tiny, triangular region in the midbrain called the lateral habenula (LHb), which acts as a junction box for signals that pass between the forebrain and other brain areas. Henn and Li's recent discoveries, published in the journal *Nature* (February 2011) suggest that the LHb might be the key to finding new treatments that could help even severely depressed patients who fail to respond to standard therapies. The scientists have found that when neurons in the LHb are hyperactive, they signal "disappointment" by crippling the brain's reward system. As Henn puts it, "What could be more depressing than that?"

## Homing in on the habenula

The CSHL team is exploring the link between the LHb and depression in rats that exhibit "learned helplessness," a set of human-like depressive behaviors

stemming from a perceived absence of control over a given situation. These animal models were developed over the last two decades by Henn, who until last year co-directed life sciences research at Long Island's Brookhaven National Laboratory. In contrast to normal rats that do whatever it takes to escape physical, life-threatening challenges, the "helpless" animals just give up and suffer passively.

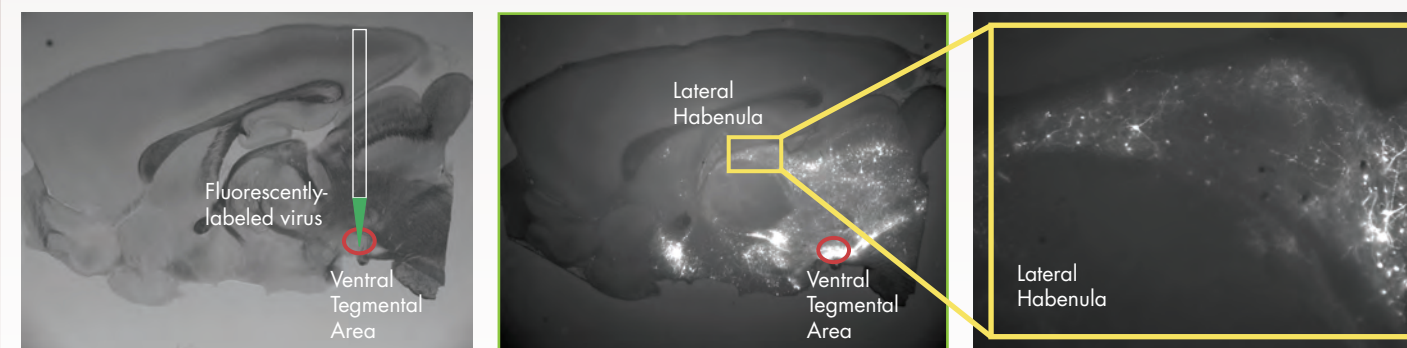
A few years ago, a study that compared these rats to those resilient to stress—Henn calls these die-hards the "New Yorker rats"—revealed a striking difference in the level of metabolic activity in just one brain region, the LHb. "Two studies by other groups had previously hinted at a connection

between 'helpless' behavior and the habenula," explains Henn. "I wanted to prove this link and define the underlying mechanisms."

To do that, Henn approached then-CSHL scientist Robert Malinow and his postdoctoral researcher Bo Li, who were just a few exits away on the Long Island Expressway. The duo also were, according to Henn, "the best team in electrophysiology," a method that allows scientists to eavesdrop on neuronal chatter by measuring electrical activity in neuronal synapses—the gaps between connecting neurons.

"Many brain areas had been implicated in depression," recalls Li. "But Fritz convinced us that the LHb was a critical target." This proved to be true right away. Li's very first recording of neuronal activity showed that the LHb neurons in depressed rats were markedly more active than in stress-resistant rats. Finding that the hyperactive LHb neurons in turn dampened the brain's reward system, "We hypothesized that if this hyperactivity occurred too often or for too long, it might not just be about disappointment anymore but rather, might cause pathology," explains Li, who accepted a faculty appointment at CSHL in 2008.

In support of this idea, the scientists found that delivering high-frequency electric pulses via electrodes inserted into the LHb (but not adjoining brain areas) of the helpless rats



When injected into a downstream target region called the ventral tegmental area (VTA), a fluorescently labeled virus illuminates depression-related neurons by entering nerve endings in the VTA and traveling to the nerves' point of origin in the lateral habenula (middle and right panels).

undid this reward-dampening effect and reduced the rats' depression-like behavior. This method is analogous to deep brain stimulation (DBS), which has helped people with Parkinson's and some with clinical depression as well.

Having used it successfully in one patient, Henn—an experienced clinical psychiatrist—is now collaborating with doctors in Germany and New York's Mount Sinai Hospital to test whether the LHb is a better target for DBS than other brain areas. Henn and Li are setting their sights on other breakthroughs, too. As Li says, "DBS is a great research tool for discovering things about depression in animal models. But for the millions of people suffering from treatment-resistant depression, there needs to be a non-invasive, less dangerous alternative."

## Solving a circuit problem

To find this alternative, Henn and Li must learn what drives the hyperactivity in the LHb; identify the targets that the LHb neurons project onto and alter in depressed animals; and ultimately, manipulate the circuitry of the LHb to halt depressive behaviors.

The LHb gets its input both from the brain's limbic system, where emotions are processed, and the prefrontal cortex, which is the brain's cognitive area. The LHb adds it all up and produces an output that affects almost all brain functions. "I think that it's this addition process in the habenula that gets jumbled up in depression," says Henn. "That's where the pathology might lie."

The team's early experiments suggest that the input that triggers LHb hyperactivity might come from the brain's glutamatergic system—a neuronal network switched on by glutamate, a powerful neurotransmitter. When glutamate molecules released into a synapse by a pre-synaptic neuron activate a post-synaptic neuron, helper cells called astrocytes end this transmission by soaking up the glutamate. Henn is

testing the idea that defects in the astrocyte re-uptake system might lead to LHb hyperactivity and depression.

Output from the LHb controls the brain's three major neuromodulators: dopamine (reward system); noradrenaline (anxiety/fight/flight response); and serotonin, which mediates a host of emotional states and is the target of almost all antidepressants available today. "But we don't know which of these pathways are affected in depression and how the target neurons alter their activity in response," explains Li. "To be able to design accurate, behavior-altering drugs, we need first to do detailed molecular studies on these neurons to understand how they're different in depression."

Li is pursuing this goal with support from the Dana Foundation and a Biobehavioral Research Award for Innovative New Scientists (BRAINS) from the National Institute of Mental Health. His methods blend classic techniques of molecular genetics and neurobiology with optogenetics, the latest innovation in molecular manipulation in which scientists use light to control the activity of individual neurons.

Working closely with other CSHL neuroscientists, Henn and Li have assembled a formidable arsenal of tools: genetically modified animals that carry light-responsive genes in their depression circuits; genetically manipulated viruses that light up entire chains of nerves and thus help trace the pre-synaptic origins and the post-synaptic targets of hyperactive LHb neurons (see image above); and more.

Although it is complex and time-consuming, defining the contours of depression's neural circuit and its components "is crucial if we are to develop more effective treatments for depression and other mood disorders," says Henn. The statistics of depression certainly bear out the urgency of Li and Henn's mission. The World Health Organization's (WHO) Global Burden of Disease project predicts that by 2020 it will become the second leading cause of illness worldwide. **Hema Bashyam**