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Josh Huang: In dogged pursuit of autism's off switch

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In 1982, **Josh Huang** was an impressionable young biology undergraduate at Shanghai's FuDan University. Like some of his fellow Chinese students, he knew he wanted to be a neuroscientist, but with limited access to scientific journals, had no idea which big questions were then at the forefront of research.

That September, a friend of his father, who was then a neuroscientist at the Chinese Academy of Sciences, showed Huang the September 1979 copy of Scientific American, a special issue dedicated to neuroscience, in the academy's library. The vivid memories of the issue, a rare color copy in "good, crisp condition" made a lasting impression on the budding scientist.

"The brain had been my interest since early on in college," says Huang. "I just didn't quite know the status of the research, how very exciting it was in the United States. It was quite an eye opener."

These days, Huang is doing some eye-opening research of his own.

At the Cold Spring Harbor Laboratory in New York, where he has **a spacious office** overlooking the southwestern tip of the harbor, Huang spends his time unraveling the intricacies of the gamma-aminobutyric acid (GABA) system, which helps dampen the activity of nerve cells in the brain. Without this filter, the brain would be over-stimulated by a constant barrage of information.

GABA is a neurotransmitter, a chemical that acts as an ‘off switch' for nerve cells. When a cell releases GABA, it travels down the length of the neuron to a synapse, the point of contact with another cell, and inhibits the second neuron from firing, or generating an electrical impulse.

GABA's dampening actions can prevent the release of other neurotransmitters, such as serotonin, and is seen primarily in the neocortex, the part of the human brain that oversees so-called higher functions such as vision and language.

Link to autism

When Huang first began studying the GABA system, he had no notion that his work might relate to diseases such as autism, schizophrenia and other neurological and psychological disorders.

"The more we learn about the development and the function of the GABA system, the more I've found that the dysfunction of this system is linked to various diseases," he says.

In individuals with autism, GABA may not effectively filter the continual stream of information from the environment[1], Huang says. "It's not that neurons are dying or that there's some gross anatomical defect. It's how they communicate that is disturbed."

Most of the nerve cells in the neocortex release glutamate, another neurotransmitter that acts as an 'on switch.' Fewer than one in five neurons in the neocortex releases GABA. But though there are fewer of them, the rich variety of GABA neurons is astonishing, says Huang.

"The neocortex is really a jungle," says Huang. The traditional anatomical approach of staining cells can't penetrate this jungle because there are so many kinds of neurons, Huang says. "They are all intermingled and connect to each other in ways that are seemingly impossible to decipher."

Huang instead applies high-resolution imaging techniques such as two-photon laser scanning microscopy and confocal microscopy to visualize neurons and synapses. In 2004, his team found that when GABA neurons send their instructions, they connect with target neurons at a specific location using certain ‘molecular labels' ? akin to the way a postal employee knows which box to put letters into because of the number on the slot[2].

"Josh uses novel and creative approaches," says **John Rubenstein**, neurobiologist at the University of California, San Francisco. "He's at the leading edge of the body of knowledge, looking at things in a different way, asking really important questions."

GABA may also play a crucial role in development. There is some evidence from Huang and others that in adolescents, the neurotransmitter controls how synapses are formed or modified[3]. A disturbance ? genetic, environmental, or both ? during early childhood might alter the way neurons are organized, making them incapable of filtering information from the outside world and leading to some of the behaviors associated with autism.

"The message is that if you disturb the GABA system at various developmental stages, it can have many different effects, both in the function and also in the assembly of the neural circuits," Huang says.

Unwavering focus

In October, Huang received a SFARI grant to explore how mutations in the MeCP2 gene ? linked to Rett syndrome, one of the autism spectrum disorders ? affect the GABA inhibitory system. "If you can understand that, then you can try to develop ways to intervene," says Huang.

MeCP2 is a DNA-binding protein that is thought to be important for the formation of synapses, and for shutting off genes when their products aren't needed[4].

Unraveling these complex relationships is enormously challenging, but if anyone is up to the task, it's Huang, says Brandeis University biologist **Michael Rosbash**, Huang's Ph.D. advisor.

Huang is one of only a handful of researchers studying GABA at a genetic level, as opposed to the more common approaches of anatomy and physiology, Rosbash notes.

Huang also never gives up.

"He's ambitious and focused, and it's been the key to his success," says Rosbash. "At the same time, he's fun and generous to other people, which makes him great to work with."

Those qualities probably served Huang well in his first few years at Cold Spring Harbor, when his genetics approach didn't deliver results, and he published few papers. "Many times it was difficult to gather breath or energy," he recalls.

One accomplished scientist even asked Huang, "Why are you doing this? There are easier, better-defined areas for a starting assistant professor to study."

But Huang was undaunted.

"I remember that period," says **Graziella di Cristo**, who for five years was a postdoctoral fellow in Huang's lab. "There was a lot of pressure on Josh, but we didn't feel it. He encouraged us to try new things," recalls di Cristo, now an assistant professor at the University of MontrÃ©al. "That kind of intellectual freedom and support is pretty rare."

The team persevered for four years ? until the breakthrough in 2004.

"There's so much that's totally unknown. If you understand how the disturbance alters development or behavior, then you understand how the brain works," says Huang. "Wow, that would be something."

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