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In future studies, the MIT team plans to investigate the effects of the amygdala on other targets in the hippocampus and the prefrontal cortex, which has also been implicated in anxiety. Deciphering these circuits could be an important step toward finding better drugs to help treat anxiety.

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Earlier this year, we welcomed the newest member of our junior faculty—Dr. Li-Huei Tsai, Ph.D., director of the Picower Institute for Learning and Memory. A leader in the field of neuroepigenetics, Dr. Tsai’s research focuses on understanding how environmental and genetic factors influence the expression of genes in the brain and how this expression affects behavior.

Dr. Tsai completed her undergraduate studies at MIT, earned her PhD at the Picower Institute for Learning and Memory.

In the study, researchers examined the role of Tet1, a protein that promotes the removal of methylation—a modification that controls access to genes. High methylation levels keep genes “off,” whereas low methylation levels allow them to be expressed.

The researchers found that mice lacking Tet1 had reduced levels of methylation in the hippocampus and the cortex, two brain regions important for memory and emotion processing. The study also showed that the activity of Tet1 is regulated by a protein called Npas4, which is needed for the memory extinction process.

The researchers conclude that Tet1 is necessary for the extinction of fear memories. They also found that mice lacking Tet1 did not show a decrease in fear responses when exposed to a previously conditioned stimulus. In contrast, mice with normal Tet1 levels showed a significant decrease in fear responses.

These findings suggest that Tet1 plays a crucial role in the extinction of fear memories and that targeting Tet1 may be a promising strategy for treating anxiety disorders.

Li-Huei Tsai, Ph.D., Director of the Picower Institute for Learning and Memory.
**How Old Memories Fade Away**

If you got beat up by a bully on your walk home from school every day for a year, you would be very afraid of the spot where you usually met him. However, if the bully moved away from town, you would gradually cease to fear that area. This is a familiar example of the process of memory extinction. Enhancing the activity of this gene, known as Tet1, can make mice less anxious in the presence of a phobia. With the help of the NIH award, she is applying her innovative impact potential. Kay has been studying the nervous system circuitry that MIT’s Department of Brain and Cognitive Sciences since January 2012—extending his experimental study of animals to groundbreaking discoveries of other genes necessary for memory extinction. “If you got beat up by a bully on your walk home, you would naturally lose that memory. However, if the bully moved out of town, you would gradually cease to fear that area.”

**Center of Memory Genes**

The researchers found that Tet1 exerts its effects on memory by altering the levels of DNA methylation, a process in which molecules called methyltransferases add a methyl group to DNA. This results in a reduced ability of the DNA to be transcribed, meaning that the gene is not expressed. The researchers found that mice lacking Tet1 had much lower levels of DNA methylation—an intermediate step in the removal of methylation—in the hippocampus and cortex, which are key to learning and memory. These changes in demethylation were most dramatic in a group of about 200 genes, including a subset of so-called “immediate early genes,” which are critical for memory formation.

In the hippocampus, many of these genes are involved in learning and memory. To measure the memories that mice with normal Tet1 levels lost their fear of the area with more open space. To measure the memories that mice with normal Tet1 levels lost their fear of the area, they had to be trained to fear it. The researchers found that mice with normal Tet1 levels lost their fear of the area with more open space.

**BRAIN CIRCUIT CAN TUNE ANXIETY**

Anxiety disorders, which include posttraumatic stress disorder, social phobia and obsessive-compulsive disorder, affect 40 million American adults in a given year. Currently available treatments, such as selective serotonin reuptake inhibitors, are not always effective and have severe side effects. To develop better treatments, a more specific understanding of the brain circuits that govern anxiety is necessary. Kay Tye, an assistant professor of biology and cognitive sciences and member of the Picower Institute for Learning and Memory, has been studying the nervous system circuitry that MIT’s Department of Brain and Cognitive Sciences since January 2012—extending his experimental study of animals to groundbreaking discoveries of other genes necessary for memory extinction.

**Memory Genes Paved**

The researchers also discovered that Tet1-deficient mice are still able to form new memories. During extinction training, the mice were trained to fear a particular cage where they received a mild shock. After a particular cage where they received a mild shock. After the training, the researchers found that mice lacking Tet1 had much lower levels of DNA methylation—an intermediate step in the removal of methylation—in the hippocampus and cortex, which are key to learning and memory. These changes in demethylation were most dramatic in a group of about 200 genes, including a subset of so-called “immediate early genes,” which are critical for memory formation.

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The Tet1 gene appears to control a small group of so-called “immediate early genes,” which are critical for memory formation. Thus, since Tet1 and other Tet proteins have the ability to regulate the expression of these genes, the researchers hypothesized that Tet proteins might control memory extinction.

"This will not only help us further delineate the mechanisms that control anxiety levels. By turning the volume of this gene up or down, we can control anxiety levels. But the new memory informs the mice that the shock will come from the beginning, not from the end of the cage,“ says Tsai, the Picower Professor of Neuroscience.

To study those interactions, the researchers turned to optogenetics, which allows them to engineer neurons to turn their electrical activity on or off in response to light. For this study, the researchers modified a set of neurons so that they would turn on or turn off when the Tet1 gene was active. When these neurons were illuminated, the researchers found that mice without Tet1 were more likely to stop and freeze in place, whereas mice with Tet1 showed less fear.

"This is a powerful tool to study memory extinction,“ says Tsai. "It allows us to test whether memory extinction is controlled by Tet proteins and whether Tet proteins can control the expression of so-called immediate early genes.”

"This will not only help us further delineate the mechanisms that control anxiety levels, but will also unravel other potential mechanisms that might be involved in memory extinction,“ says Tsai.

The researchers found that if mice lacking Tet1 had much lower levels of 5hmC in the hippocampus, they were more likely to remember the fear stimulus and react with anxiety.

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One day in 2011, Kwanghun Chung, while a post-doc at Stanford, put half a mouse brain on top of the label of a container of saline solution and showed everyone in the lab how they could read the label right through the tissue.

Chung had invented a chemical treatment that keeps organs intact while rendering them transparent.

CLARITY, as its creators call it, has been called one of the most important advances for neuroanatomy in decades. Its possibilities--tracing specific neural circuits, illuminating cells and subcellular structures, exploring how proteins, nucleic acids and neurotransmitters interact, for starters--extend far beyond labor-intensive, error-prone reconstructions of two-dimensional brain slices.

Chung, known as KC, joined MIT this year. In addition to his appointment as a Picower principal investigator, he is building a lab as an assistant professor for the Institute for Medical Engineering and Science (IMES) and the Department of Chemical Engineering.

There’s a palpable buzz about CLARITY. A handful of labs in the UK and the US are already experimenting with making see-through brains. A recent workshop at the Picower Institute led by members of the Chung lab drew participants from Princeton, Harvard, the University of Utah, as well as labs within MIT. “We want to train people to use this technology for their research,” Chung said.

**A Clear View**

While it’s been known for decades that lipids are the culprit that renders brains opaque, simply removing the lipids turns the tissue into soup, Chung said. His unique approach is to replace the lipids with the kind of transparent hydrogel commonly used in biology to separate and study proteins.

After a sample brain is zapped with an electrical charge and fixed with formaldehyde, it sits for days in a hydrogel bath that, when heated to around body temperature, forms a mesh that holds the tissue together but doesn’t bind to lipids. The lipids are then washed away with detergent.

Fluorescently labeling neurons, axons, dendrites, synapses, proteins, nucleic acids, layers of the cortex or inner structures of the brain illuminates them; commercially available software renders the data in 3D and you’re left with a spectacular light show in a box, where a subset of astrocytes, excitatory neurons, and inhibitory neurons are represented by brilliant blues, greens, and smears of pink. The excitatory neurons undulate like green cilia or hair-thin fiber-optic cables with glowing neon tips.

Chung hopes to use CLARITY to see physical and chemical differences between diseased brains and healthy brains. “We don’t know which components and circuits are abnormal in many brain disorders. In Alzheimer’s and Parkinson’s, specific types of neurons die; while others—the same cell type in the same brain region—are fine. There are so many things we don’t know about neurodegenerative and neurodevelopmental disorders,” he said. “I want to pinpoint those abnormal components to help us understand the underlying mechanisms and develop new therapeutic strategies. This technique helps us extract more complete information from the brain.”
Complex Interactions

In a study published in 2011, Tye found that activating a different subset of neurons in the amygdala had the opposite effect on anxiety as the neurons studied in the new paper, suggesting that anxiety can be modulated by many different converging inputs. “Neurons that look virtually indistinguishable from each other in a single region can project to different regions and thus have opposite effects on anxiety,” Tye says. “Anxiety is such an important trait for survival, so it makes sense that you want some redundancy in the system. You want a couple of different avenues to modulate anxiety.”

The Neuron study contributes significantly to scientists’ understanding of the roles of the amygdala and hippocampus in anxiety and offers directions you want some redundancy in the system. You want a couple of different avenues to modulate anxiety.”

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In future studies, the MIT team plans to investigate the effects of the amygdala on other targets in the hippocampus and the prefrontal cortex, which has also been implicated in anxiety. Deciphering these circuits could be an important step toward finding better drugs to help treat anxiety.

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**RESEARCH HIGHLIGHTS**

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