Ki Goosens finds a potential new therapy for PTSD and other stress-related illnesses
Ki Goosens had been studying the amygdala, the seat of emotional memory in the brain, since her undergraduate days at the University of Virginia in the early 1990s. And happily so—as she finished her doctoral work at the University of Michigan, she was hoping to spend her life contributing to her field and to the textbooks of the future.

Then, just after Goosens began a postdoctoral fellowship at Stanford University in 2002, two members of her family developed mental illness. What struck Goosens most profoundly was how few treatment options the doctors could offer. “I was frustrated and angry,” she says.

In both cases, the symptoms had been triggered by major life stressors. “I thought, I know something about
stress,” recalls Goosens. “I have this power
I’m not using. That was a huge turning
point for me.”

From that point on, Goosens, now an assistant
professor of brain and cognitive sciences at
MIT, committed herself to finding ways to
improve the lives of people with mental
illness. By the time she joined the McGovern
Institute in 2006, she had settled on a
strategy. She would take a fresh look at the
effects of stress on the amygdala. Having
studied this brain structure from many angles
—molecular, cellular, and behavioral—
Goosens knew there was a puzzle waiting
to be solved.

Now, seven years later, her work has uncovered
a promising new drug target for stress-induced
mental illness. Having found a new bio-
chemical pathway that controls fear learning,
she is now collaborating with researchers at
Massachusetts General Hospital to plan a
clinical trial with the aim of preventing stress-
induced relapse of major depressive disorder.
“The most important follow up we’re doing
is to move towards a treatment,” she says.

**Thriving Under Stress**

At the time Goosens began working on
stress, the field was focused on two sets of
stress hormones produced by the so-called
hypothalamic-pituitary-adrenal (HPA) axis.
These hormones, the glucocorticoids and
catecholamines, had long been thought to
coordinate the stress response. Given the
importance of stress as a risk factor for
mental illnesses, it was natural to assume
that drugs targeting the HPA axis might
be beneficial. Yet the results of clinical trials
had been disappointing, suggesting that
something was missing from the picture.

Sensing that the field was in a rut, Goosens
decided take a new approach. She looked to
the amygdala for clues because, she explains,
“there is something special about how the
amygdala responds to stress.” In many other
parts of the brain, stress is detrimental to
neurons, causing deterioration and damage.
In the amygdala, however, neurons seem
to thrive under stress, and Goosens wanted
to know why.
She began searching for brain genes whose expression was affected by stress. One that caught her attention was the gene for growth hormone, which was elevated by stress in the amygdala but not elsewhere. This well-known hormone circulates in the blood and induces growth in bone and other organs. However, it cannot cross the blood-brain barrier, so there had been little reason to look for effects on brain tissue.

When Goosens realized that amygdala neurons were actually producing their own growth hormone, she suspected it might be the cause of their growth under stress. To test this idea, she developed genetic methods to increase growth hormone artificially within the amygdala. Postdoc Anthony Burgos-Robles had recently joined her lab, and he performed the experiment to examine the relationship between amygdalar growth hormone and fear. The result was that the animals became excessively fearful. “The effect was huge,” says Goosens, who likens the behavior to post-traumatic stress disorder. She had found her first clue.

Follow the Data

In 2007, shortly after joining the McGovern Institute, Goosens presented her work during an MIT-sponsored boat cruise in the Boston Harbor. In the audience sat graduate student Retsina Meyer. “Ki presented so many different experiments and different techniques,” recalls Meyer. “I wanted that kind of variegated experience for my graduate work.” Meyer, who completed her PhD in 2013, shared Goosens’ desire to make life better for people with psychiatric disorders. She became the first graduate student to join Goosens’ lab.

By the fall of 2008, Goosens had already made a connection between growth hormone and another circulating peripheral hormone called ghrelin. Originally named for its ability to induce growth hormone release, ghrelin is also recognized as a hunger hormone that can stimulate appetite. Ghrelin is produced in the gut, and unlike many other hormones it can cross the blood-brain barrier to affect the brain.

So Goosens and Meyer began a series of experiments to explore the relationship between stress, ghrelin and fear learning. An early surprise was that ghrelin, like growth hormone, could increase fear, but only if it was given chronically; a single dose did not enhance fear.

“We decided to just keep perturbing the system to see what happens,” says Meyer. They tested the effects of chronic stress by immobilizing rats for several hours each day, which makes the animals more prone to develop fearful memories—a model for human post-traumatic stress disorder (PTSD). The chronically stressed animals were more fearful as expected, and they also had elevated levels of ghrelin in their blood.

Meanwhile, Goosens asked Burgos-Robles to examine the connection between ghrelin and growth hormone. He used a viral vector to artificially express a growth hormone antagonist in the amygdala, and showed that this blocked the fear enhancing effects of repeated ghrelin stimulation. The techniques were new to Burgos-Robles, so Goosens trained him. “From day one, she was at the bench with me,” he says.

As the links between stress, ghrelin, growth hormone, and fear grew stronger, Goosens and Meyer decided to perform a key experiment to determine whether ghrelin was necessary for the rats to develop PTSD-like increases in fear. Meyer gave the animals a drug to block ghrelin signaling, and again exposed the animals to chronic stress before testing their ability to learn fear.

The drug completely blocked the stress-induced increase in fear, confirming that ghrelin is not merely incidental, but a central player in stress-induced fear learning.

At this point, Goosens and her team had more than enough unexpected results to publish several papers, but they felt compelled to collect more. “We didn’t have the whole picture,” says Goosens. “We’d get another piece of the puzzle, and then we just kept adding to it.”

The biggest surprise was still to come. To find out whether ghrelin was working via the known stress hormones—glucocorticoids and catecholamines—Meyer surgically removed the adrenal glands that produce these hormones, and tested the effect of chronic stress on fear learning and ghrelin levels. If the surgical procedure blocked the stress-induced changes, it would imply that ghrelin was a component of the known HPA pathway—an interesting discovery, but not
revolutionary. “But if the fear response persisted—well, that would be something really new,” says Goosens.

Sure enough, stress-related increases in fear and circulating ghrelin persisted undiminished, despite the complete removal of the known stress pathway. This meant that Goosens and Meyer had discovered a novel pathway for stress-induced fear that is completely distinct from the HPA pathway. The work has just been published in the journal *Molecular Psychiatry*. Most importantly, it points to a potential new therapeutic strategy for preventing the effects of chronic stress on the brain.

**Solving the Puzzle**

Goosens has already filed two patent applications through the MIT Technology Licensing Office: one with Meyer on the use of anti-ghrelin agents to prevent or treat stress-sensitive psychiatric illness, and another on the use of anti-growth hormone agents for the same purpose.

Ghrelin is a particularly exciting target because drugs have already been developed to block it. Though they didn’t pan out for their original purpose of preventing obesity, these drugs have proven to be safe in clinical trials. “Pharma companies have these compounds on their shelves,” says Meyer, who is now looking for a scientific position in the industry. “What we want to do is repurpose them for psychiatric disorders.”

Goosens now has two projects underway to explore the role of ghrelin in human mental health. In one, she is working with the MGH Center for Anxiety and Traumatic Stress Disorders to measure ghrelin levels in the blood of patients with fear and anxiety disorders. The first samples have just arrived, and results should start to emerge soon.

She is also collaborating with MGH researchers to launch a clinical trial of an anti-ghrelin drug to prevent relapse in major depressive disorder. “Relapse in this disorder is almost always triggered by stress,” says Goosens, who received funding for the trial in July and is currently working through the approval process.

While ghrelin has dominated Goosens’ work for the last several years, she has also been launching other projects. For instance, Burgos-Robles is studying how the electrical activity of the amygdala changes during prolonged periods of stress. The initial studies are performed in rats, but the eventual hope is to find human biomarkers linked to the cumulative effects of stress, which may in turn predict a person’s risk of developing PTSD or other stress-related conditions. “For patients who have not yet passed the pivot point, we could try to prevent the disorder,” says Goosens.

Goosens is also examining gene expression in brain samples from individuals who committed suicide and comparing them to brains of individuals with no history of mental illness. The project is funded by the Army Research Office (ARO) through the Defense Advanced Research Projects Agency (DARPA), which is interested in the biological basis of resilience under stress.

The technologies have come a long way since Goosens first entered the field, but the big questions remain, and her overall approach remains unchanged. If there’s a clue hidden in those brain slices, Goosens intends to find it and to use all the experimental power she can muster to solve the puzzle.
New Gift to Support Neurodegeneration Research

Rose and Douglas C. Barnard ’79 have made a generous gift to support neurodegeneration research at the McGovern Institute.

The Barnards believe strongly in the value of basic research, which is one reason they have chosen to support the McGovern Institute. The other reason is more personal. Both of Rose’s parents struggled with neurodegenerative diseases.

“It is critical to find the true cause of neurodegenerative disorders like ALS, Alzheimer’s and Parkinson’s,” says Rose Barnard. She and her husband also believe that there will be plenty of opportunities for clinical research once scientists have determined the underlying causes.

The Barnards hope that their gift will help McGovern scientists explore the fundamental mechanisms underlying neurodegenerative disorders and ultimately pave the way for new treatments and earlier diagnosis of these diseases.

For information about making a gift to the McGovern Institute, contact Kara Flyg at 617-324-0134.

New Center for Intelligence Research

McGovern Investigator Tomaso Poggio is leading a major new project to understand the basis of intelligence. The Center for Brains, Minds and Machines (CBMM) has been established with a $25M grant from the National Science Foundation, and will be headquartered at the McGovern Institute. The five-year project will bring together scientists from MIT, Harvard, Cornell and other institutions, with the goal of understanding the basis of biological intelligence and replicating it in machines.

Computers have become remarkably successful in solving many specialized tasks, from interpreting speech to playing chess or Jeopardy. But the highest ambition of artificial intelligence—the development of machines that can match human performance in real-world situations—remains largely unfulfilled. Even the most sophisticated computer systems struggle to interpret complex visual scenes or to manipulate real-world objects with dexterity—tasks that even young children can perform with ease.

Now is the time to revisit those early ambitions, according to Poggio. “We know much more than we did before about biological brains and how they produce intelligent behavior. We’re now at the point where we can start applying that understanding to the design of intelligent machines.”

The center will focus on four broad themes: integrating intelligence across domains such as vision, movement and language; neural and electrical circuits underlying intelligence; the development of intelligence in children; and social intelligence. In each area, computational models and biological studies will go hand in hand. “With a system as complicated as the brain, we need to get people to work together across different disciplines and techniques,” says Poggio.

Several McGovern faculty members have already joined the project, including Ed Boyden, Robert Desimone, Nancy Kanwisher and Rebecca Saxe, along with researchers from 17 institutions in the US and worldwide. The new center will also partner with companies such as Google, Microsoft, IBM and others, to explore potential commercial implications of the research.
Ki Goosens’ lab has discovered that the hormone ghrelin—known as the “hunger hormone”—may also be a key to post-traumatic stress disorder (PTSD). Ghrelin released during chronic stress makes the brain more susceptible to fearful memories, suggesting that drugs that block ghrelin may lessen the effects of chronic stress (see feature story on pg 2).

John Gabrieli’s lab, in collaboration with Boston Children’s Hospital, has identified brain differences in young children that could help predict dyslexia. In a study of 40 kindergarteners, poor pre-reading skills (a known predictor of dyslexia) were correlated with structural differences in the left arcuate fasciculus, a large bundle of fibers that connect brain areas involved in speech production and comprehension.

Ann Graybiel and colleagues found that the brain concentration of the neurotransmitter dopamine rises gradually as rats navigate a maze in search of reward. A similar mechanism in humans could explain our ability to remain focused on distant goals in the face of distraction.

Feng Zhang has previously described a new method for genome editing, based on a bacterial nuclease system called CRISPR. Now, in a further development, Zhang’s group has modified the method to make it up to 1500 times more accurate, potentially removing a key barrier to future clinical applications.

Evelina Fedorenko and Nancy Kanwisher, along with John Duncan in the UK, have mapped a network of brain regions that are activated by many kinds of demanding mental tasks. These so-called multiple demand regions are interspersed between other brain regions that are specialized for particular functions such as language, number processing or face recognition.
Brains on Trial with Alan Alda

Nancy Kanwisher and Rebecca Saxe were featured in Brains on Trial, a two-part PBS television special that explores the role of neuroscience in the criminal justice system. On September 17, the show’s host, Alan Alda, came to the McGovern Institute to moderate a public discussion based on the PBS program. Panelists included Robert Desimone, Joshua Greene, Nancy Kanwisher, Bea Luna, and Stephen Morse. A video and photo album of the event is available on our website.

The McGovern Institute for Brain Research at MIT is led by a team of world-renowned neuroscientists committed to meeting two great challenges of modern science: understanding how the brain works and discovering new ways to prevent or treat brain disorders. The McGovern Institute was established in 2000 by Patrick J. McGovern and Lore Harp McGovern, who are committed to improving human welfare, communication and understanding through their support for neuroscience research. The director is Robert Desimone, who is the Doris and Don Berkey Professor of Neuroscience at MIT and former head of intramural research at the National Institute of Mental Health.

Further information is available at: http://mcgovern.mit.edu