

WARDROBE CHANGE NUMBER 9

BY CARA MASSET

INSIDE THE WORLD OF OCD

The alarm went off at 6 a.m. Instantly, the question pushed into Hilary Zurbuch's head: *What am I going to wear?* She slipped out of bed in precisely the same manner that she did every morning, getting out on the right side. Then she approached her closet, the question still pounding: *What am I going to wear?*

Zurbuch, a 30-something woman, picked out an ensemble, then pressed it under a hot iron. Something wasn't right. Although the khakis and plaid shirt were fine last week, today they just didn't *feel* right. No, she couldn't wear this to her job. Zurbuch picked out another pair of slacks and a collared shirt. Ironed those. *Would this make me look like I'm 12?* she wondered. Scratch that. Zurbuch decided on another outfit. Ironed it. Would she look perfect in this? She wanted to look perfect. Plus, she felt that nagging fear she's had since childhood that if her outfit wasn't just right, something *bad* would happen that day.

It was the same wicked dread that led Zurbuch to quit crayons and coloring books for good as a preschooler because she thought she might fail to color perfectly. The fear that she'd been *bad*, and that it would be her fault if *bad things* happened to her parents or siblings. The fear that if she didn't turn around 16 or 32 times before getting into bed, things would go bump in the night.

A woman with obsessive compulsive disorder shares the story of how she was paralyzed by the decision of what to wear each morning, among other concerns. Intensive exposure therapy helped her get out of the OCD trap. But that therapy is difficult to pursue. Pitt's Susanne Ahmari is revealing the brain workings of this painful condition in hopes of finding other effective therapies.

PHOTOGRAPHY | CAMI MESA



ABOVE: Compulsions often manifest as rituals, like excessive ironing. OPPOSITE PAGE: Zurbuch got out of bed in precisely the same manner every day. As a child, she believed that if she didn't turn around at least 16 times before getting under the covers, something terrible would happen.

Nearly two hours have passed, and Zurbuch is still in her apartment, selecting clothes, ironing, and starting over again. *What am I going to wear?* She has to be at work in an hour, and she's still not dressed for the job. She hasn't eaten breakfast.

The kitchen. She hasn't gone into the kitchen. Not the kitchen. Not today. She can't handle the fear that *something awful* will happen if she enters the kitchen. Sometimes the fear leads her to skip meals. She won't tell a soul about the distressing thoughts invading her brain. But maybe someone could help her get through the morning.

She calls a friend. *Can you help me get breakfast?*

Zurbuch is a young professional who holds a master's degree, golfs regularly, takes annual pilgrimages to the beach with friends, volunteers in her community, and laughs a lot. She's also a person living with obsessive compulsive disorder (OCD).

The disorder is characterized by a tug-of-war between obsessions and compulsions. In OCD, obsessions are intrusive, often fearful thoughts, like Zurbuch's fear that she'll have a bad day if she doesn't choose the right outfit in the morning. Compulsions are repetitive behaviors or rituals that people with OCD often engage in to try to control their obsessions. Initially the rituals may provide temporary relief from the fixations, but as they become more frequent, the actions can disrupt daily living and become embarrassing and exhausting. Even though many people with OCD may recognize that their compulsions are senseless, they engage in them for hours at a time.

What happens in the brain to lock people with OCD into their rituals is still not known. A team of researchers at the University of Pittsburgh is using clinical observations and new neuroscience tools to extricate a deeper understanding of the disorder. Led by Susanne Ahmari, an MD/PhD and assistant professor of psychiatry in the School of Medicine, the team is striving to help patients like Zurbuch who have, at different periods in their lives, become consumed by OCD. The disorder has been cited by the World Health Organization as one of the 10 most handicapping conditions because of decreased quality of life and loss of income. The Burroughs Wellcome Fund and other organizations have recognized Ahmari's approach to studying the mysteries of obsessions and compulsions.

In its investigations, Ahmari's team is primarily using mouse models. It is among the first in the world to equip the mice with a tool that's blowing the neuroscience field away: a mini-microscope that can record activity in real time from hundreds of neurons. "What this allows us to do is, basically, to have streaming video from the brain of a mouse," Ahmari says in awe. "I never could've imagined this technology in grad school." (That was in the late '90s and early '00s.)

The mini-microscopes were, in fact, developed at the institution where she attended grad school—Stanford University—but they were only dreamed up in the years after Ahmari had moved on to a residency and faculty position at Columbia University. When she was at Stanford, using electrodes to obtain signals from single neurons was cutting edge.

Ahmari's excitement over the newest tech developments in her lab may come from growing up in a family of engineers. "My first rebellion was to become a biologist," she says, joking. The family engineers wonder how she can work with messy, living things rather than clean, logical devices like microchips. *How can you stand it?* they tease.

Ahmari stands it just fine. In fact, she revels in it. She pursued her bachelor's degree in biochemistry and biology close to her home, Chicago, at the University of Illinois at Urbana-Champaign, where as a freshman she won a Howard Hughes fellowship. As she perused the faculty laboratory list, she was immediately intrigued by a research lab studying learning and memory in the brain.

The lab was headed by the late William Greenough, who was among the first psychologists to demonstrate that the brain is a flexible organ that can change with exercise and other enriching experiences. He was, she recalls, a fabulous mentor who encouraged her to follow a career in research. She worked in his laboratory at Illinois throughout her undergraduate career, planning all along to continue on to graduate school and earn a PhD.

Then, Ahmari learned about MD/PhD programs, and began to consider a wider path that would make the family engineers proud, but a little squeamish, too. "I always knew the reason I wanted to do research was to help people," she says, adding that she was concerned that, by solely earning a PhD and working in a laboratory environment, she would never meet any of the people who might be helped by her research. So she decided to get an MD, as well.

During the research portion of the MD/PhD program at Stanford, Ahmari studied synapse formation at the molecular and cellular levels in the hippocampus brain region. Although it was valuable and exciting work from a basic neuroscience perspective, she says



it made her realize that she would prefer to apply her lab skills to examining poorly understood illnesses. Many of her neuroscience MD/PhD peers elected to pursue neurology residencies; she chose the more unusual direction of specializing in psychiatry.

The outfit was horrendous. A mashup nightmare. The sort of getup that only a 4-year-old could pick out and unabashedly wear in public: purple paisley boots, Captain America socks, plaid pajama pants, a Superman T-shirt, and a knit toboggan cap. The cringe-inducing combination of garments upped Zurbuch's anxiety. Not only was the color combo hideous, but the clothes hadn't been ironed. And now she was being dared to walk. In front of others. Wearing *that!*

Zurbuch's therapist gently coaxed her to go out in the unironed, absurd outfit. On one level, Zurbuch knew that she could walk out of the room in her ridiculous garb and everything would be fine, just like she knew that wearing two shades of violet to work probably didn't mean she was a bad person. On another level, she felt paralyzed. It felt physically impossible to step outside in the hideous outfit. Like when she tried to tell herself that it would be okay to go to the grocery store or enter her kitchen, but the wicked dread stood in the way of even hunger and won.

Then, finally, Zurbuch put one purple paisley boot in front of the other and walked out the therapy center door. She made it down the hallway before her anxiety stopped her from going farther. Another day, she wore the outfit outside the therapy center. Later, she and her therapist walked farther from the building, where strangers were passing by. Finally, after a month, Zurbuch went grocery shopping with her therapist. Wearing that. And her anxiety level, well, it had gone down to about a 2 out of 10. Everything, Zurbuch recalls, was okay.

During her psychiatry residency and subsequent fellowship at Columbia, Ahmari was exposed to patients with a range of mental illnesses. While treating patients with OCD, she was surprised and humbled by how severe and debilitating the disorder was. For instance, at one point in her life, Zurbuch was in the grip of obsessions or compulsions nearly constantly.

Ahmari learned that the treatment options available for OCD are limited. The family of drugs most commonly used to treat mental health conditions—selective serotonin reuptake inhibitors (SSRIs)—only provide remission in approximately 10 percent of OCD patients and mild-to-moderate improvement in 30 to 50 percent, she says. There's also exposure therapy, which makes patients confront their fears—as Zurbuch did when behavioral therapy coaches sent her out in public in a mismatched outfit. "Patients who are able to complete the treatment can have great results from this, but it's incredibly difficult for patients to do," Ahmari says. And qualified therapists with enough time in their schedules to offer exposure therapy are not always available. Although there are good services in Pittsburgh, Zurbuch traveled to Boston, staying three months, because she required intensive and lengthy therapy.

So Ahmari began hunting for other solutions. In her work as an assistant professor of clinical psychiatry at Columbia, Ahmari began focusing more on treating patients with OCD; she also dove into neuroscience research on the disorder. "I've found clinical care incredibly rewarding," says Ahmari. "Independent of [my] research's impact on people's lives, I get the reward of helping people to use the tools at their disposal—medications, therapy, their own inner resources. Even more so, what I really love about the patients that I've worked with is that they're very interested in the research. They're very motivated to understand what is happening in their own brains. Why can't they stop themselves from performing these compulsions?"

In the lab at Columbia, Ahmari conducted a study on OCD circuitry that yielded surprising results and landed publication in *Science*. The 2013 paper described her team's use of a mouse model to test whether hyperstimulating circuits in the brain's orbitofrontal cortex (involved in decision-making) and ventromedial striatum (involved in selecting particular actions and responding to rewards) would lead to increases in OCD behavior. The team chose to examine those parts of the brain because prior imaging studies had shown homologous areas to be hyperstimulated in patients with OCD. However, no one was quite sure whether the hyperstimulation actually led to OCD symptoms or was a compensation for the symptoms. (Maybe that was just the brain's attempt to fight off the domineering thoughts.)

For the study, Ahmari applied a method known as optogenetics. (That technology was brought to you by Pitt's 2015 Dickson Prize in Medicine winner, Karl Deisseroth; see p.

On one level, Zurbuch knew that she could walk out of the room in her ridiculous garb and everything would be fine, just like she knew that wearing two shades of violet to work probably didn't mean she was a bad person. On another level, she felt paralyzed.

6.) It worked like this in Ahmari's lab: Her team used a virus that's darn good at getting inside cells—an adenovirus, which typically causes ailments like the common cold. The virus's genetic code had been engineered to include a pigment called channelrhodopsin that's sensitive to light.

Ahmari's team injected the virus into the orbitofrontal cortex of the mice. The virus wriggled its way into the neurons—including through long projections to the ventromedial striatum; and because the virus was carrying the light-sensitive channelrhodopsin with it, the entire neuron became sensitive to light.

Step two of the process was to surgically implant tiny fiber-optic probes into the mouse brains. The probes allowed the research team to shine light into the brains to activate the light-sensitive neurons in the regions associated with OCD.

Ahmari and her colleagues expected that when they hyperstimulated the orbitofrontal cortex and ventromedial striatum circuits, they would immediately see more OCD behavior—in this case, excessive grooming by the mouse. But nothing happened. At least not initially. They did eventually see compulsive grooming behavior, but only if they stimulated the circuits for a few minutes daily for several days.

This unexpected finding, Ahmari says, provides some insight into her own clinical observation and the observations of other psychiatrists that OCD symptoms may gradually emerge over time. It seems that relevant brain regions are first repeatedly activated by triggers in the environment. The paper's findings may reveal more of the wiring of OCD, creating a map to ultimately help pharmaceutical researchers find better drug treatments.

For people with OCD, triggers can range from monumental incidents, like the death of a parent, to everyday slights, like a friend teasing about a bad hair day. In an hour-long BBC program on OCD that aired in September and featured a segment on Ahmari's research, one patient who was interviewed described the trauma of having a friend in middle school casually mention that she had sour breath. The shame replayed itself in her mind, and she became obsessed with her breath. Rituals emerged for brushing her teeth, using mouthwash, and popping breath mints.

Obsessions can be very selective. Zurbuch would stress for hours over her outfit, for example, but hardly think about her hair. During behavioral therapy, her therapists actually encouraged her to get a haircut and pay more attention to her blond locks.

The same year that the *Science* paper was published, Ahmari was recruited to Pitt by David Lewis, chair of the Department of Psychiatry, the Thomas Detre Professor of Academic Psychiatry, and director of the Translational Neuroscience Program.

"She's developed a research program that begins with observations made clinically about the nature of obsessive compulsive disorder and then converted those observations into hypotheses about the nature of the underlying brain disturbances, which she has been testing in elegant experimental models and animals," Lewis, an MD, says.

Ahmari calls her peers in the Translational Neuroscience Program a "wonderful group" of supportive, idea-bouncing colleagues and says that she has been impressed by the rich collaborative environment of the Pittsburgh neuroscience community. "It's not the case everywhere," she says. "It was extremely attractive to go to a department that had a shared vision and a goal of using the newest, most powerful technologies for attacking this really important [mental health] problem," she says.

Since arriving at Pitt, Ahmari has devoted her time to setting up her laboratory in the Bridgeside Point II building along the Monongahela River in South Oakland. She has begun hiring and training postdoctoral fellows and graduate students—another area where she excels. "She's not only really good in training individuals in the conduct of science but also in how to think as a scientist," Lewis says. "It's not just about learning how to do something at the bench but about how to think and also about how to behave and interact with other scientists. A lot of people want to come and work with her because she has all those things. She's a magnet for mentees."

One of Ahmari's first mentees is James Hyde, a postdoctoral associate who holds a PhD in neurobiology and developmental science. "She's an incredible mentor. She has a psychiatry background and brings that to bear when it comes to training her students. It helps with figuring out how to approach a behavioral problem," he says. "She's also a very precise, very exacting researcher. And she has a very large research network. If there's something I don't know, she knows someone who does."

Hyde has been tasked with the coolest job in the lab: running experiments with the mini-microscopes and mouse models. The microscopes build upon the optogenetics technique that Ahmari used in her *Science* paper. With the microscopy technique, rather than injecting a virus engineered with channelrhodopsin into the mouse brains, Hyde injects a virus engineered to encode a molecule called GCaMP6. This protein creates a burst of light (fluoresces) in the presence of calcium. Because calcium is one of the primary molecules that neurons take up when they send and receive signals, neurons treated with the GCaMP6 protein will flash every time they fire.

Hyde then surgically implants tiny base plates into the mouse skulls. During experiments, Hyde connects miniature microscopes weighing only 1.9 grams to the base plates. The microscopes are lightweight, so the mice can run around as they normally would; that's a big advancement over other technologies that require animal models to be fixed in one spot. The microscopes contain cameras like the ones in smartphones, so Hyde can record the flashing neurons.

"What's astounding is the combination of things in these tiny microscopes," Ahmari explains. "Now we're not looking at one neuron at a time. We can look at up to 200 neurons at a time, and we can look at them over the course of weeks or months. The microscope can peer inside the brain . . . and we can see what language or code they're using when engaging in behaviors related to OCD." The technology is so advanced, she says, that her research team can watch communication between groups of neurons or individual neurons. It's like having the ability to listen to an

For people with OCD, triggers can range from monumental incidents, like the death of a parent, to everyday slights, like a friend teasing about a bad hair day.

entire orchestra—then choosing to listen to one section of violins or cellos—and homing in even further to hear every single player on a solo level.

"The other real innovation comes in the acquisition of data," she adds. One recent morning, Hyde recorded brain activity in two mice for 30 minutes. The recordings yielded 100 gigabytes of data. He offloaded the data sets onto the lab's workstations to process them during the next 24 hours. The next day, Hyde sent the data to a statistics team at Carnegie Mellon University that has been building algorithms and suggesting ways to fully comprehend all the information.

The Carnegie Mellon team, headed by statistics professor Robert Kass, is part of the Center for the Neural Basis of Cognition, a joint venture between Pitt and CMU. Kass and Ahmari began collaborating this year.

Kass says the new mini-microscope approach is among the more exciting recording technologies coming online for neuroscience. And it's generating more information than ever before. "It's in the realm of what we call Big Data these days," he says.

Yet it can be difficult to assess all of the information. That's where he can help. "It's easy to find patterns in data that seem to give you an explanation of something, when actually what you're looking at is random stuff. If you're not careful, you can't tell the difference. The challenge in statistics is to say, how much do we know from this data?"

"The collaboration has been so critical for us," says Ahmari.

So far, Ahmari's team has just preliminary results from the mini-microscopes. The research will be funded during the next three years through a $75,000 McKnight Scholar Award from the McKnight Endowment Fund for Neuroscience. Only six scholars nationwide were selected for the 2015 award, which is reserved for young scientists who are establishing their labs. Ahmari is looking forward to attending a meeting for McKnight awardees next summer, along with fellow 2015 McKnight awardee Marlene Cohen, a Pitt PhD assistant professor of neuroscience who studies how visual attention guides behavior.

Next year, Ahmari also hopes to be able to set up a clinical practice and start seeing OCD patients again.

Patients have raised important research questions for Ahmari. She notes that one patient told her "the experience of having anxiety relief from performing a compulsion was extremely rewarding even though having the obsessions and compulsions was not rewarding at all." That got Ahmari thinking about the neural pathways involved in reward. What are those pathways like in a brain dealing with OCD?

In recent months, Elizabeth Manning, a postdoctoral associate in Ahmari's laboratory, has been conducting some experiments related to reward. Clinical observations have shown that OCD patients often struggle to adapt to new situations, Manning says. Even when rewards are involved, it's difficult to change behavior. Manning has shown this through a test in optogenetic mouse models.

Manning trained mice to push one of two levers. If they pressed the correct one, they would receive a chocolate pellet. Initially, the left lever produced the chocolate, so the mice learned to push that one. Later, the right lever became the magic button for chocolate. The mice displaying typical behavior would learn to push only the right lever within a day or two. The mice displaying OCD-like behavior, however, were unable to adjust their behavior for as long as a week to get the chocolate prize.

Manning wonders, were the reward circuits underactive or overridden by hyperactivity in other areas? And they'll be exploring which neural circuits were involved.



Zurbuch plays nine holes every day; it helps her live in the moment. Her grandmother, who made her this children's golf bag, started teaching her how to golf when she was 8.

On a golf course, Zurbuch concentrates on the ball near her feet. She swings and pops the ball into an arched trajectory toward the green. She watches it land, then carries her bag toward it. Hitting the ball, watching it land, inching closer to the hole—these are the only things she thinks about while on the course. There are no added rituals. There are no obsessive thoughts. She is only thinking about the here and now. Golf.

Zurbuch's grandmother taught her to golf in the backyard when she was 8 years old, and she took up the sport more regularly in college. She now tries to get out for at least a nine-hole round every day. Zurbuch says that golf relaxes her and has helped her to become healthy; it creates a space for her to practice the art of mindfulness, of living in the moment.

In the winter, when golf courses are dormant under snow, Zurbuch has found that she's able to practice mindfulness through cooking. As a result of her hard work in intensive exposure therapy sessions, she's no longer afraid of the kitchen. And she can get dressed without panicking or changing 10 times. Some of her obsessions still show up, but they've faded into the background, like when you become desensitized to the sound of a ticking clock. When the obsessions become louder, she is confident that she doesn't need to pay attention to them.

This year, Zurbuch, now a licensed behavioral therapist, opened a private practice. After years of studying, training, and improving her own health, she specializes in helping children as young as 3 overcome OCD, anxiety, and phobias through evidence-based treatments. "I love being a therapist," she says. "It's the best job I could possibly have in the world. To understand the depths of OCD and the pain . . . and then to help people . . . is very rewarding [and] unbelievable to me from where I was at."

On her desk, she keeps a box of her grandmother's golf balls. It's a reminder of what Zurbuch calls the beauty of the game: If you swing and miss or send the ball into a bunker, it's okay.

All you have to do is adjust your grip and swing again. ■