Hopkins BrainWise
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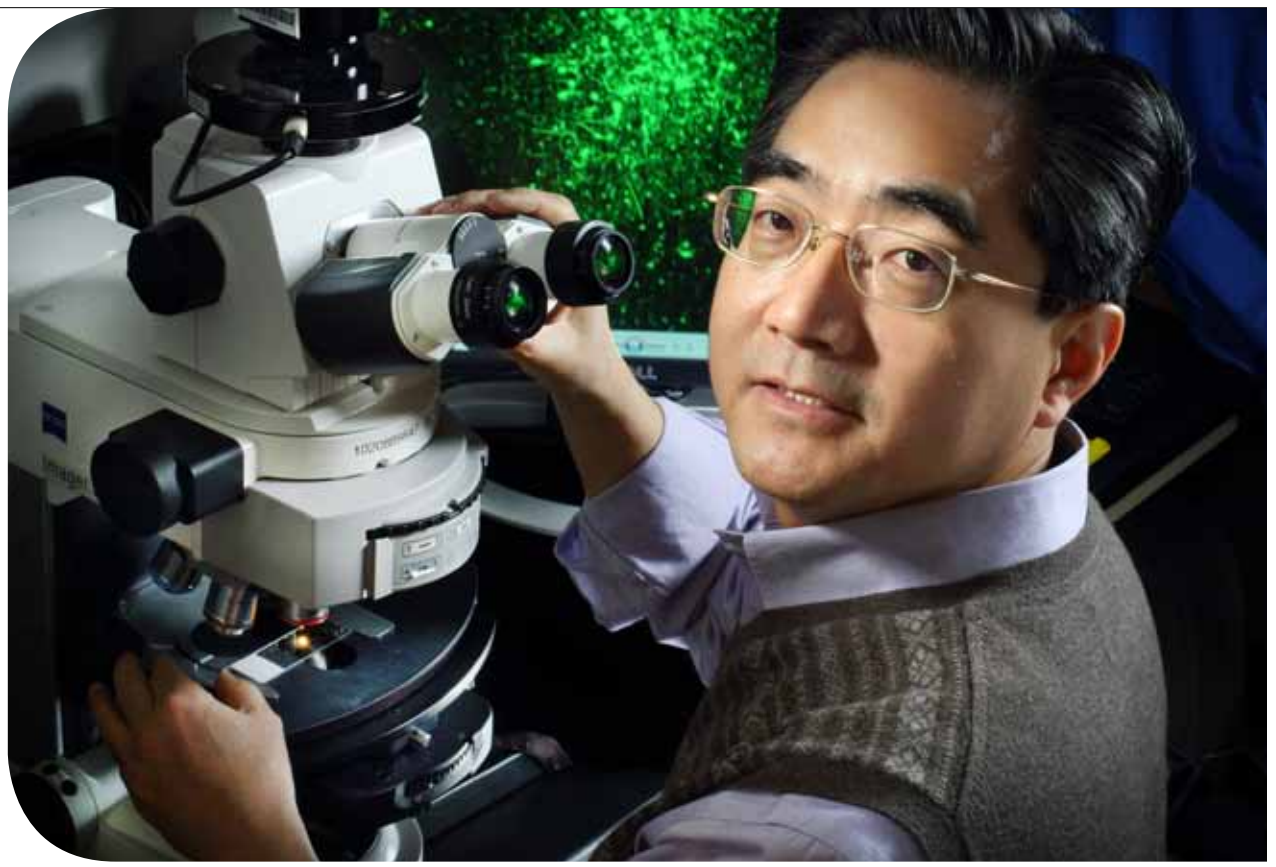
White Fat, Brown Fat, Bad Fat, Good Fat



For nearly two decades, Sheng Bi and colleagues have been teasing out neural signal pathways in rat brains that transform white fat into calorie-burning brown fat. The research has drawn great interest for its potential to treat obesity and diabetes.

When psychiatry researcher **Sheng Bi** came to Johns Hopkins from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in 1999, he studied impaired glucose tolerance in a rat model. In trials comparing the feeding of obese and normal rats, he analyzed gene expression in obese rats with abnormally large appetites or diabetes. But when he looked at tissue from the obese rats' brains, he noticed something interesting: an increase in the appetite-stimulating neuropeptide Y (NPY) protein.

That chance finding kick-started years of research in the department's Behavioral Neuroscience Lab, in which Bi and colleagues have been teasing out neural mechanisms underlying the controls of food intake, energy expenditure and glucose regulation.

In a 2011 study in the journal *Cell Metabolism* that garnered attention from the BBC and NPR, Bi and his team found that knocking down NPY expression in the dorsomedial hypothalamus of the brain—which helps regulate thirst, hunger and body temperature—not only reduced rats' calorie intake and weight, but also transformed their fat into a type that burns off more energy.

The study looked at two types of fat made by the body: white and brown adipose tissue, or WAT and BAT. WAT is the typical fat that ends up around our middles and other places, and stores the extra calories we eat. These cells have a large droplet of lipid as an energy storage unit. Cells in BAT, considered a "good fat" for its energy-burning qualities, contain many mitochondria (cell powerhouses) and little droplets of lipid, each with its own power source, which generates heat. Babies have ample stores of brown fat at birth to help protect them against cold, but it mostly disappears, so adults have very little of this calorie-burning tissue.

Checking the rats' fat content after death, Bi was surprised to find brown fat in the groin area of the rats with knocked-down NPY in place of where white fat should be. The transformation may result from an activation of BAT stem cells contained within WAT tissue, he says, so brown fat doesn't actually disappear with age but becomes inactive.

While the critical role for brown fat in adults in the maintenance of energy balance remains to be determined, Bi says, finding it in adults has "led to a great interest in its potential for treating obesity and diabetes, such as searching for ways to elevate brown fat activity or turning white fat to brown fat that would burn calories instead of storing them."

Continuing work by Bi's team, funded by NIDDK, has found that knocking down NPY can reverse diet-induced obesity and impaired glucose tolerance in rats.

In a study published last fall in the *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology*, Bi investigated a rat model of high-fat, diet-induced obesity and insulin resistance designed to mimic human obesity with impaired glucose regulation. Rats had free access to either regular or high-fat chow and underwent an oral glucose tolerance test. Then, some received injections of a recombinant virus to knock down NPY expression.

The control group of rats untreated with this recombinant virus remained obese, glucose intolerant and insulin resistant, whereas those treated with the recombinant virus saw a complete reversal of conditions within weeks. They exhibited normal food intake, body weight, glucose tolerance and insulin sensitivity like normal, lean rats.

NPY expression seen in rats is similar to that observed in primates, Bi says, so if these types of studies can be replicated, the protein expression could serve as a potential target for the treatment of obesity and diabetes in humans. ■

Learn more about Sheng Bi at **bit.ly/ShengBiJohnsHopkins**.

"If we could get the human body to turn 'bad fat' into 'good fat' that burns calories instead of storing them, we could add **a serious new tool to tackle the obesity epidemic** in the United States."

— SHENG BI

Behavior Change: Can It Predict AD Onset?

There's no mistaking that Alzheimer's disease poses a major threat: Some 5.3 million Americans live with the disorder—a number likely to double over the next 20 years as baby boomers age.

Well aware of that, a team of Johns Hopkins psychiatrists has spent years teasing out which early patient symptoms foreshadow an Alzheimer's diagnosis. Certain signs of functional loss (problems driving, forgetting to pay bills) or slips in cognition (word loss, forgetfulness) seem most reliable.

Now, growing evidence suggests that psychiatric (behavioral) symptoms can also be Alzheimer's predictors. "For many years, we've been working backward—treating Alzheimer's as a purely cognitive disease," says **Paul Rosenberg**, associate director of the Johns Hopkins Memory and Alzheimer's Treatment Center. "But behavioral changes can be widespread and disabling," and pose the greatest challenge to caregivers.

"So, when I hear a spouse say, 'My husband has never been a worrier, and now he frets over everything,' or, 'He used to be interested in everything and now has no get-up-and-go,' I have good reason to think Alzheimer's is involved."

The scenario is common enough that Johns Hopkins scientists, working with an international consortium, have coined the term "mild behavioral impairment" (MBI) to describe neuropsychiatric symptoms that can accompany, and possibly even predate, Alzheimer's cognitive lapses.

In recent clinical studies, Rosenberg, Memory Center Director **Constantine Lyketsos** and colleagues used the Neuropsychiatric Inventory Questionnaire to reveal trends in several psychiatric symptoms. For example, they found newly irritable or apathetic seniors 30 to 40 percent more likely to develop Alzheimer's. "It wasn't so surprising seeing MBI in people already mildly cognitively impaired," says Rosenberg, "but that risk also applies to those who appear cognitively fine."

Paul Rosenberg and colleagues have found that behavioral change can accompany—and even predate—Alzheimer's better-known cognitive lapses.

The biology underlying Alzheimer's behavioral symptoms is far from clear. But, surely, damage to specific nerve circuits is involved. And they likely overlap other, better-known Alzheimer's pathways, Rosenberg adds, such as those for salience—the ability to judge something's importance.

As for therapy, present research hopes to shed light on how behavioral interventions work. For now, to alleviate symptoms, Rosenberg favors lifestyle changes, like stress reduction programs, yoga and exercise, over traditional psychiatric approaches.

Rosenberg's "big-picture dream," is to nail down who's at risk for Alzheimer's. "Our best chance of making a difference," he says, "is to assess as early as possible." The near future should bring far fewer expensive brain scans and pedigree searches. Instead, he says, "We expect to combine cognitive tests, gene assays and other low-tech ways to diagnose Alzheimer's."

Mild behavioral impairment, of course, will be part of the mix. ■

Learn more about assessing the probability of dementia: **bit.ly/alzheimersrosenberg**. And learn more about the Johns Hopkins Memory and Alzheimer's Treatment Center at **hopkinsmedicine.org/psychiatry/specialty_areas/memory_center/**.

Neuropsychiatric Symptoms in **Alzheimer's Disease**

Mild
- depression
- anxiety
- irritability
- apathy
- disinhibition

Severe
- agitation
- aggression
- aberrant vocalizations
- hallucinations
- euphoria

Source: Paul Rosenberg

When Adolescent Angst Morphs into Depression

Irritability, angry outbursts, eye-rolling—all are hallmarks of adolescence. But at what point do negative emotional behaviors go beyond teenage snark to signal clinical depression?

The question isn't trivial, says psychiatrist **Leslie Miller**, who has made answering it a focus of her practice and clinical study. The need to catch depression early in a demographic known for high suicide risk drives her work. If clinicians could pinpoint when subtle changes in behavior raise the risk of mood disorders, she says, what a boon that would be.

For now, in intake interviews, Miller notes any possible predictors, their frequency and when, or if, there's been descent into depression. Miller directs MAP, the established Johns Hopkins Mood Disorders in Adolescents and Young Adults Program. Its research and successes with patients at such vulnerable ages—most between 12 and 22—first depend on parents referring their children.

Yet adolescence itself slows referrals.

Teenage paths to depression often don't mirror those of adults. Rather than sadness, for example, irritability and angry outbursts may dominate. Also, for some adolescents, dark moods appear less intense. Says Miller: "A parent will say to me, 'My daughter often smiles. Or laughs! How could she be depressed?' Teens, however, can be very good at hiding what's going on."

Movie Chronicles Life with Manic Depression

Filmmaker Paul Dalio has experienced many ups and downs with bipolar disorder. Diagnosed at age 24, Dalio spent five years in and out of psychiatric facilities and was despondent over his situation until he read psychiatrist **Kay Jamison**'s book *Touched with Fire*, in which Jamison discusses the links between manic depression and creativity. It was a refreshing change from the clinical books he had found.

A meeting with Jamison at one of the hospital cafeterias further inspired him to get healthy.

"She told me she didn't know one artist who wasn't more creative after having bipolar than before, as long as they're on meds," Dalio says. "She told me I would feel certain things I didn't think I would feel, like exuberance. It was life-changing because it gave me hope for the first time that I didn't have to kill myself and go through hell or just wait around lifelessly waiting to die. I could find something that was in between. And that was what launched me on the change in my journey."

Now stable on medication for years, Dalio, son of New York investor Ray Dalio, a donor to the Department of Psychiatry and Behavioral Sciences, wanted to chronicle the experience of bipolar disorder in a film. In an ode to Jamison, it, too, is called *Touched with Fire*.

The movie, released in limited theatres nationwide last February, features actors Luke Kirby and Katie Holmes as two poets with bipolar disorder who meet in a psychiatric facility and start a relationship. The film takes the audience on a journey through the highs and lows of bipolar disorder and how it affects not only individuals but their friends, families and work life. Jamison's book is featured prominently, and she makes a cameo appearance as herself, advising the protagonists in her own words. Spike Lee, Dalio's professor at New York University Film School, served as executive producer.

Dalio screened the film at Baltimore's Charles Theatre in December as part of the Johns Hopkins University School of Medicine Psychiatry and the Arts Series. The showing was followed by a discussion featuring Dalio, Jamison and psychiatry Director **J. Raymond DePaulo Jr.**, Dalio's physician during his last hospitalization in 2007.

The movie is "so authentic as to be a bit disturbing to some people," DePaulo says, including a rarely seen but accurate portrayal of "the angst and desperation of parents that I see all the time. That was very compelling."

Several attendees at the screening told DePaulo that they hoped for a storybook ending, which he says he got from seeing Dalio: "He looked anything but manic—he was calm, he was thoughtful, he spoke carefully. He was generous and also very humble. People really got it—that this was a really unbelievable transition that occurred over several years. For a psychiatrist, there's nothing that gives you such deep gratification as seeing a recovery of a full life, far beyond symptom resolution."

Dalio has never been more creative, DePaulo says. He not only wrote and directed the film but also wrote the musical score.

Says Dalio, "I hope [the movie] allows people to appreciate something other than a clinical illness, so that instead of pitying people or turning away from them—which only makes people with mood disorders want to hide in shame and adds to stigma—[they will] see something beautiful and redeeming and even be able to admire them for their gifts." ■

Dalio returned to Johns Hopkins on April 19 with his wife, Kristina Nikolova (a cinematographer on the film), to discuss a patient's perspective of mood disorders at the 30th Annual Mood Disorders Research/Education Symposium.

Learn more about specialized clinical services at the Johns Hopkins Medicine Mood Disorders Center at **hopkinsmedicine.org/psychiatry/specialty_areas/moods/**. Learn more about the film at **bit.ly/touchedwithfiremovie**.

Filmmaker Paul Dalio was diagnosed with bipolar disorder at age 24. Six months later, he read Kay Jamison's book, which proved transformative, inspiring him to turn it into a movie. Above, the two discuss the film over coffee. At left, Dalio with Jamison and Dalio's wife, cinematographer Kristina Nikolava.

"Teens and young adults have trouble seeing gray," says psychiatrist Leslie Miller. And in a world of black versus white, seeing only the black can put them at risk.

Often, by the time patients arrive, their negative emotional responses have escalated to depression or disruptive mood dysregulation disorder, another mood illness. In the latter, chronically irritable youths erupt in anger truly out of proportion to a situation.

Part of the challenge, then, Miller explains, is getting everyone on the same page. In the first family interview, she asks young patients, "Have you ever had thoughts about not wanting to live?" Hearing yes stuns parents. Yet frankness, she says, can be crucial in helping them appreciate where things stand.

Assessing patients with skill, of course, guides what treatment paths to choose. And in querying teens about mood, sleep habits, social withdrawal or any form of self-harm, Miller also builds their trust.

It's a clinically diverse MAP team that pools both observations and insights to design each patient's plan. Most combine medication and research-based psychosocial approaches, such as interpersonal psychotherapy. Role-playing, for example, and helping teens recognize wayward ways of communicating and problem-solving readies them to tap the power of positive encounters with others to improve mood. Dialectical behavioral therapy and cognitive behavioral therapy are also at hand.

Miller also believes—and evidence shows—"that including families from the start is essential to successful treatment. You can involve families and still honor a patient's autonomy and independence."

Learn more about the clinic: **bit.ly/adolescentmooddisordersjh**.
Watch a video with Leslie Miller: **bit.ly/lesliemilleronkidsmooddisorders**.

PAPER TRAIL

A Sampling of **Brain Research and Thinking** Underway at Johns Hopkins

A critical period of vulnerability to adolescent stress: epigenetic mediators in mesocortical dopaminergic neurons. **Minae Niwa, Richard S. Lee, Teppei Tanaka, Kinya Okada, Shin-Ichi Kano, Akira Sawa**. *Human Molecular Genetics* 2016 Apr 1;25(7):1370-1381.

Central transthyretin acts to decrease food intake and body weight. **Fenping Zheng, Yonwook J. Kim, Timothy H. Moran, Hong Li, Sheng Bi**. *Scientific Reports* 2016 Apr 7;6:24238.

Failure to upregulate Agrp and Orexin in response to activity based anorexia in weight loss vulnerable rats characterized by passive stress coping and prenatal stress experience. **Gretha J. Boersma, Nu-Chu Liang, Richard S. Lee, Jennifer D. Albertz, Anneke Kastelein, Laura A. Moody, Shivani Aryal, Timothy H. Moran, Kellie L. Tamashiro**. *Psychoneuroendocrinology* 2016: May;67:171-181.

mADAP | A Mobile App for Adolescent Depression Awareness

We are pleased to announce the release of mADAP, a video-based mobile health app based on the Adolescent Depression Awareness Program (ADAP), developed by

adolescent psychiatrist Karen Swartz. The free app is available to download in the Apple App Store. Search for "mADAP." Learn more at **bit.ly/AdolescdepADAP**.

HONORS

"A Century of Compassion," the video created for the Johns Hopkins Department Psychiatry and Behavioral Sciences to mark its centennial in 2013, has won a gold CINDY (Cinema in Industry) Award from the International Association of Audio Visual Communicators. The cinematographer was Richard Chisolm and film editor, Kindall Rende. To view the video, visit **bit.ly/100thanniversaryjhpsychiatry**.

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