Explorations and revelations taking place in the medical school

Moderate activity builds up the brains of older adults.

BRAIN TRAIN

EXERCISE STRENGTHENS THE MIND, TOO

BY ELAINE VITONE

When a rodent takes an exercise wheel for a spin regularly, new brain cells sprout up and flourish, synapses form, dopamine and serotonin spike, and new vasculature spreads. In maze challenges, cardio-mice are superior in learning and retention, compared to their couch-potato contemporaries.

It's hard to know exactly what's going on in living, breathing, exercising human brains at the cellular level since dissection is not an option. But for the last decade, Kirk Erickson—a Pitt professor of psychology with a secondary appointment in medicine—has studied brain imaging to better understand the effects of physical activity on brain structure as well as function, both emotional and cognitive.

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He's found that, of all the available approaches for enhancing brain health, exercise is one of the most promising, "if not *the* most," he says.

Back in 2011, Erickson helped confirm that the human hippocampus—which is critical to memory formation, linked to dementia, and known to deteriorate with age—actually bulked up in older adults who increased their activity for a 12-month stint.

And here's the kicker: All they did was regular, moderate walking.

One of the big remaining questions was exactly how much moderate activity is necessary to achieve these effects, says Erickson. "We don't have a very good answer at this point." And in a $22 million National Institutes of Health (NIH) funded study currently under way, he hopes to find out.

The study, dubbed Investigating Gains in Neurocognition in an Intervention Trial of Exercise (IGNITE), is enrolling adults between the ages of 65 and 80, some of whom are already experiencing some memory and cognitive losses, to participate over a 12-month period. The participants will be assigned three different levels of exercise intensity. The team will study changes in their cognitive performance and MRI markers of brain health, with the goal of determining whether those changes are dependent on "dose" or intensity of activity. Erickson also hopes to gain insight into whether age, genetics, or changes in the nervous system, heart, and metabolism mediate any brain gains.

For reasons no one quite understands, African Americans are at a heightened risk for early cognitive losses and have higher rates of dementia. Recently, Erickson received a five-year NIH grant to evaluate several ways of combating decline. Three times a week for six months, one group of older African American study volunteers will take an African dance class; another will take a course in African culture, cooking, and music. The idea is that both classes have a social aspect as well as cognitive stimulation, but only the dance class will include physical activity. (All of the above are known to improve brain health.)

Erickson has his fingers in a lot of pies. He's also collaborating with Catherine Bender, endowed professor in oncology nursing and director of the PhD program in Pitt's School of Nursing, to examine whether physical activity can fend off the cognitive deficits that accumulate in women undergoing breast cancer treatment.

In yet another collaboration, Erickson is teaming up with Terrence Forrester at the University of the West Indies in Mona, Jamaica. Forrester's studies have shown that malnutrition in childhood causes extremely persistent deficits in emotional and cognitive functioning, all the way up through adulthood. Together, the duo is conducting a pilot study investigating whether physical activity in such adults could improve mood, cognition, and brain health.

"For all of these adults now who had childhood malnutrition," Erickson says, "are their cognitive deficits kind of locked in and not very malleable, or can they be modified in any way? It's a really important question." ■

GUSTAVO FRAZAO/GETTY IMAGES

FAIR WARNING

A BETTER WAY TO PREDICT OVERDOSE

BY KRISTIN BUNDY

PHOTO: GETTY IMAGES. TYPOGRAPHY: ELENA GIALAMAS CERRI

As the opioid epidemic rages on, the Centers for Disease Control and Prevention reports that there are about 130 overdose-related deaths per day in the United States.

Despite the ongoing crisis, Walid Gellad, a Pitt physician and health policy specialist, says, "We just don't have a good way of identifying" who is most likely to overdose. For example, Gellad notes, the way Medicare's current risk algorithm is set up, 70 percent of overdoses occur in their low-risk group and 30 percent in their high-risk group.

"We typically think that people on high dosages of opioids are at high risk of overdose," says Gellad. But that's just a risk factor—not a risk prediction. "Not everyone on a high dosage will overdose."

Risk prediction, on the other hand, digs deeper to examine the many facets of life that might influence risk. "You can have two people on the same dosage, but one can have a low risk of overdose because they've had a stable day, they've been on that dose for a long time, they don't have a psychiatric illness, they don't have a substance use disorder, and they didn't just get out of jail. Someone else might be the exact opposite."

Gellad's work sorts through these details. As associate professor of medicine and of health policy and management and director of Pitt's Center for Pharmaceutical Policy and Prescribing, Gellad develops risk-prediction models for opioid overdose using machine learning.

Earlier this year, Gellad and his team published findings on the risk of overdose three months after Medicare patients were prescribed an opioid.

The algorithms successfully captured 90 percent of the overdoses in the medium- and high-risk groups. And overall, 75 percent of the participants were found to be low risk, which surprised Gellad. "We expected many more. . . . Because, in clinical practice, we're treating a lot more people as high risk."

Gellad, who is also an internist at the VA Pittsburgh Health System, says this heightened perception of risk leads to a burden of hypervigilance among those who need prescription opioids and take them safely. Patients, no matter their risk classification, must provide urine samples at each visit and answer questions like: What dosage are you taking? How often do you fill your prescription? Do you have naloxone at the ready? Gellad says, "If we can alleviate this burden in people with a low risk of overdose, it will have a big impact."

To that end, Gellad is conducting machine-learning studies on risk prediction and opioids. In one study, which is funded by a $1.8 million grant from the National Institutes of Health, the investigators are using Pennsylvania Medicaid claims to predict opioid overdose (and other outcomes) and explore other ways of modeling the data.

Another study is funded by the Richard King Mellon Foundation. In collaboration with Pitt's Graduate School of Public Health and the Allegheny County Health Department, Gellad is applying machine-learning techniques to county services datasets. These include Medicaid claims, 911 calls, court records, jail records, child-welfare records, and coroner reports—all scrubbed of information identifying individuals.

This anonymized information, says Gellad, might help paint a more complete picture of overdose risk versus health care data alone. "There's a thought that acute events in someone's life are related to overdose," he says. Through this collaboration, the researchers hope to better equip the county in allocating support services to those who need them. ■

COURTESY ERIK WRIGHT

In nature, superbugs are super rare. Wright's team hopes to learn new tricks from microbes that have been keeping them in check for millions of years.

TAKING CUES FROM SOIL

BY JACOB WILLIAMSON-REA

THE DIRT ON ANTIBIOTIC RESISTANCE

Each year, 2 million people in the United States battle an antibiotic-resistant infection, and of those, 23,000 die. As cases of antibiotic resistance continue to rise, the race is on to introduce new antibiotics to save these patients.

The solution might be just beneath our feet.

Most therapeutic antibiotics come from bacteria that naturally produce antibiotics. "Thousands of these antibiotic-producing bacteria live on a barely visible speck of soil," the University of Pittsburgh's Erik Wright notes. They've been producing antibiotics to protect themselves for millions of years.

Surprisingly, in the natural world, resistance has remained at astonishingly low levels, says Wright, an assistant professor of biomedical informatics. With a $1.5 million Director's New Innovator Award from the National Institutes of Health, Wright hopes to learn a few of nature's tricks.

"We want to know how soil bacteria have avoided antibiotic resistance for so long, and how that might inform our clinical use of antibiotics."

Clinical and agricultural antibiotic use consists of one antibiotic compound at a high dose. The natural antibiotic producer *Streptomyces*, however, uses small amounts of many different antibiotic compounds, specifically tailoring them to individual threats. "This led us to consider a nature-guided approach, or biomimicry," Wright says.

Wright will use mass spectrometry, which details chemical structures of molecules and will allow the team to analyze how different streptomycetes respond to threatening microorganisms. The researchers can then watch how *Streptomyces* changes defensive-compound secretions: what exactly each streptomycete produces, whether bacteria target competitors as groups or individuals, and more.

Additionally, by comparing the DNA sequences and other genomic features of organisms, he'll study the synergistic potential of *Streptomyces*. Natural antibiotic cocktails produced by different streptomycetes might have frequently occurring compounds that appear together, which would suggest certain combinations are more successful.

"Maybe we'll discover information that we wish we had well before we started using antibiotics," says Wright. "Or maybe this will encourage us to take a step back to understand how best to use them.

"The dream is that this research will lead to the use of antibiotic cocktails, instead of individual compounds. This would allow us to not only tailor treatments, but possibly make antibiotic resistance a thing of the past." ■

Editor's Note: In our next issue, catch more news on the drug-resistant bacteria front: Phage viruses, from a Pitt lab, cured a life-threatening infection in a double-lung transplant patient.