Pitt people are showing how helpful it is to keep a big-picture perspective when approaching illnesses of all kinds—especially when the nervous system, including its master regulator, is part of that picture.

THE BIG PICTURE

MIND IS MATTER, PART II

BY ELAINE VITONE

A lot of docs bristle at terms like *holistic*, so evocative of crunchy, feel-good sales pitches that turn out to be thin on science. Yet evidence abounds of the link between the mind and the body. Notably, as we featured in our last cover story, Pitt investigators have mapped the neural network from a visceral organ all the way to the brain for the first time; that finding was published in *Proceedings of the National Academy of Sciences* (*PNAS*) in August.

Our organs don't live in vacuums, after all—they are part of the whole living, breathing *us*—and the systems of our bodies are in constant cross-talk. Hence it's no wonder that, for example, people with schizophrenia are more likely to have heart disease. Or likewise, that when you heal one ailing aspect of your being, the benefits can have a rippling effect.

Sometimes, potential cures are hiding in unexpected places.

In this second installment of our two-part brain-body-ography, we find out how valuable it can be to approach illness with a big-picture perspective.

ARTWORK | GREG DUNN

GUT FEELINGS

The placebo effect can be potent. In clinical trials for functional bowel disease, it's huge—to the tune of 40 to 50 percent. (In some areas, like cancer treatment, it's negligible.) Why are placebos so powerful in the GI realm? Because in many cases, the source of the problem isn't in the gut at all.

"The signals being sent to and fro, [from the brain] to the GI tract, are deranged, and you can't see that," says Pitt's David Levinthal (PhD '04, MD '06, Fel '12), assistant professor of medicine and director of UPMC's Neurogastroenterology and Motility Center. "It's just something that's essentially invisible to standard medicine. And that's the world of psychosomatic medicine, in a nutshell."

Levinthal coauthored the *PNAS* paper that was the focus of the first half of this double feature. That study mapped the neural anatomy connecting the brain to the adrenal gland—and paved the way for a more mechanistic understanding of psychosomatic illness.

Now, Levinthal is exploring the brain's links to the stomach and colon. So far, he's presented his preliminary findings at meetings for the Society for Neuroscience, the American Psychosomatic Society, and the American Neurogastroenterology and Motility Society.

In these and other organs Levinthal and his Pitt colleagues are studying, a common theme is emerging. Each organ appears to have neurological "siblings," if you will, elsewhere in the body. For example, the adrenal gland is controlled by a brain region that also controls core muscles. That insight has caused an *aha!* moment for the neurobiology community: If the adrenal gland—which is part of the stress response—and the core are both plugged into the same part of the brain, suddenly it makes sense why people swear by the stress-busting effects of exercises like yoga. Perhaps strengthening the one "sibling" can help fortify the other. And perhaps doing right by the "kids" can be good for the "parents," too. Because it's all part of the same network. One big, happy family.

In Levinthal's preliminary data, the colon appears to have a neuroanatomical sibling, as well—the leg musculature. And if you've ever been stuck in a hospital bed, or a cast, or anything else that has limited your walking-around time, that's a potential *aha!*, too.


Davis


Gianaros


Levinthal

"It's well known that immobility is on the short list of things that cause constipation," says Levinthal. And that amounts to much more than just discomfort—the wait for the bowels to come online and back to working order can lengthen post-op stay, Levinthal reminds. "It's important to establish that [function] before you let someone out of the hospital."

As for the stomach's neurological family tree, it's a bit more complicated. In Levinthal's rodent studies, the stomach appears to have two "parents" in the brain. One parent is a brain region that is also the parent of your adrenal gland's fight-or-flight response system. And the other parent? It's a brain region that governs the vagus nerve, which is a truly odd duck in neuroanatomy. Your vagus nerve is giant, extending from the brain stem itself all the way down and through you, influencing virtually everything about your physiology. "It's a visceral-sensory, visceral-motor, general-sensory, and skeletal-motor nerve all wrapped up in one," says Levinthal. (Talk about a Big Brother.)

So this "parent" brain region shared by the vagus nerve and the stomach—the insula, as it's called—is a seat of higher-order functions like emotion, cognition, empathy, and decision-making. "Which is really interesting," Levinthal says. Think fainting at the sight of your own blood or at the mere sight of a syringe: that's your vagus shutting you down.

Vagal responses, as these spells are called, can befall you with all sorts of triggers, from prolonged standing to low blood sugar to the prick of a needle, and the mechanisms of how all of this works are still unclear. Yet, says Levinthal, "Clearly, mind matters."

Similarly, the gut-churning nausea we feel in moments of emotional upheaval, like embarrassment, shock, or sudden loss, may well be the work of the vagus—the stomach's sibling.

The vagus-stomach network is "very clear" in Levinthal's rodent studies, and so far it's holding up in early studies of nonhuman primates, too. And now, with funding from the National Institute of Diabetes and Digestive and Kidney Diseases, Levinthal is undergoing training in a technique called transcranial magnetic stimulation (TMS), a noninvasive tool that will eventually allow him to safely map these neural networks in humans. Using a rapidly moving magnetic field that induces a current, TMS makes it possible to actually stimulate specific neurons on the surface of the brain from outside of the skull.

"You could use TMS as a probe, as a tool, to influence the system, and then measure some of those effects at the stomach level, or the colon, or other organs," he says. Eventually, he hopes what he learns will inform a new therapy possibility for people with the debilitating GI diseases he sees in his clinic every day. TMS is already FDA approved for patients with depression.

Additionally, this work is giving the team a new window into what brain areas may be involved in regulating the vagus, that super-nerve so broad in its reach and so mysterious in its impact.

HEAD AND HEART HEALTH

In the '70s and '80s, we had a stereotype for a heart attack waiting to happen: a rage-filled, perpetually rushed, competitive,

short-fused guy that we called a type A personality. This hypothesis launched an explosion of research, which, over time, revealed a more nuanced understanding of stress and cardiovascular disease. Really, hostility was the important part of this cardiovascular caricature—and you don't have to be a workaholic businessman to suffer its cardiovascular effects. Further, the research community found, factors like social support—or lack thereof—play important roles, as well.

For decades, the University of Pittsburgh has been among the top institutions studying stress and cardiovascular disease; Pitt has one of the oldest training grants in cardiovascular behavioral medicine in the country. Its director, Distinguished Professor of Psychiatry Karen Matthews, and her fellow Pitt giants in this field—J. Richard Jennings, Stephen Manuck, Thomas Kamarck, Anna Marsland, and Matthew Muldoon—have been at the forefront of disentangling such heart-health influences as psychosocial factors, genetics, environment, immune response, development, and age.

This rich head/heart-health history is part of what drew Peter Gianaros here 16 years ago as a postdoc—he then got a National Institutes of Health award and stayed. "I can't imagine being anyplace else in the world," he says. "We have leading neuroscientists and leading researchers in cardiovascular behavioral medicine in one place."

Gianaros, now a professor of psychology and psychiatry, studies the neurological basis for the sort of mental stress that sets blood pressure to the boiling point. Using fMRIs, he's working to establish the brain signature of people who develop stress-related cardiovascular disease, which he hopes might eventually be a way to flag people at risk. Gianaros has found that one brain region in particular lights up in those who have especially amped-up cardiovascular responses to stress: the anterior cingulate cortex. Recently, that very same region was also found to be hardwired to the interior of the adrenal gland—the body's stress-hormone factory—in nonhuman primates (as detailed by Levinthal with Pitt's Peter Strick, the Thomas Detre Professor, chair of neurobiology, and scientific director of the Brain Institute, and Richard Dum, a research associate professor of neurobiology).

Gianaros was excited to learn this particular finding holds up across species. "It just shows how [studies in animals and in humans] go hand in hand to converge on the ground truth," he says.

Gianaros is also interested in how residing in socioeconomically disadvantaged neighborhoods can affect people's hearts and heads.

In recent years, investigators at Pitt and elsewhere have found that poverty truly is hazardous to your health, Gianaros notes. One study published in *PLOS ONE* in 2015 by Pitt's Mijung Park with Charles Reynolds and colleagues suggested it may even shorten our telomeres—molecular measuring sticks for our life expectancy. (See p. 30 for more on Reynolds's influential work on mental health.)

In a sobering paper forthcoming in *Cerebral Cortex*, Gianaros's team studied people who live in high-unemployment, low-income Pittsburgh neighborhoods. The team found that these Pittsburghers not only are more likely to have risk factors for heart disease, but they also have reduced levels of gray matter, especially in the brain's cortex—and these trends may not be happening independently of each other.

Granted, cause and effect is tricky to establish in observational studies like this. But, Gianaros says, one widely accepted maxim in medicine is that red flags for cardiovascular health—like elevated blood pressure, cholesterol, and glucose—are dangerous for the brain, too. In this study, the team noticed a troubling pattern in the production of the stress hormone cortisol among study participants. The researchers hypothesized that stress physiology "might be negatively affecting the brain, not just the heart or other organs of the body," says Gianaros. He's planning further studies to put these ideas to the test.

"The take-home message," he says, "is that what's bad for the heart is definitely bad for the brain, and disadvantaged areas create an environment that may be bad for both."

In the decades since the type A hypothesis, behavioral medicine and biological psychiatry have "exploded," says Gianaros, not only because now we have the technological tools to draw these connections, but also because the global health concerns of our time so often overlap.

"I think that people are gaining appreciation that a lot of disorders of the brain don't exist in isolation from disorders of the body," he adds.

"The signals being sent to and fro, [from the brain] to the GI tract, are deranged, and you can't see that. It's just something that's essentially invisible to standard medicine."

OH, THE (SENSORY) NERVE

About seven years ago, Brian Davis, a pain biologist, was studying a mouse model of pancreatic cancer when he noticed something odd. The tumor cells were releasing growth factors that bound to the sensory nerves within the pancreas, spawning massive neural growth and sensitization and making a bad situation even worse. What's more, the cancer then began to damage the nerves, causing them to send molecular distress signals to the immune system. Which then caused the kind of excessive inflammation that is *itself* cancer fueling.

"It wasn't a huge leap for us," says Davis, a PhD professor of neurobiology and medicine. "Sensory neurons drive inflammation; inflammation drives cancer. So what if we get rid of the sensory neurons?"

The team injected capsaicin—a natural, nerve-snuffing component of the chili pepper—into young mice with pancreatic cancer genes, wiping out much of their sensory nerves. "We didn't think it would stop the

The environment that sensory nerves create can determine whether cancer lives or dies.

cancer. We hoped that, at best, it would slow it," Davis says.

They were astonished to find that disease progression ground to a halt—especially in the mice who had almost all of their sensory nerves nulled. Though the animals did develop precancerous lesions, the tipping point never came. The study was published in *PNAS* in March 2016.

In December, Davis and his colleagues published a review paper in *Trends in Neurosciences* showing this was no fluke, making a damning case for nerves as cancer conspirators in humans. And in the realm of animal research (on prostate, stomach, and skin cancer), the team notes that such high-profile journals as *Science*, *Science Translational Medicine*, and *Cell* have published findings that—sometimes in metastasis, and sometimes even in forming a primary tumor in the first place—cancer fails to get a foothold when sensory nerves are out of the picture.

This unexpected new direction in Davis's research has underscored for him just how underappreciated our sensory fibers are. In fact, some pain biologists have given them a new name more befitting their status: metaboreceptors. Calling them pain fibers is "demeaning," he says—they're better than that.

Perhaps, he says, "their normal day job is to help maintain peripheral tissues, to keep them healthy. They interact through the release of small molecules to coordinate the homeostatic mechanisms that every tissue needs. This is their real 9-to-5 job." And then, occasionally, they let you know you are sick or have an owie.

Neurons of all stripes communicate with one another about our sensory input, automatic functions, and motor movements, Davis explains. The brain integrates all of this information and sends descending input right back down through our bodies—including, if we're so unlucky, to tumors.

And this is where stress comes in.

"We *know* it's a bad prognosticator for cancer patients," says Davis. "We *know* that if you can control stress, if you use drugs that keep patients from being all freaked out, they do better."

The fuel to the fire that is cancer, he says, is "a very holistic kind of a thing." ■