**A Pitt team is the first to map the neurocircuitry connecting a visceral organ (the adrenal medulla) to the brain. Researchers throughout the neuroscience community are calling this a landmark finding that will help scientists understand more about how what we are feeling and thinking influences other aspects of our health.**



# MIND IS

THE CIRCUITRY OF THE BRAIN-BODY CONNECTION

BY ELAINE VITONE

# MATTER

Just about every field of medicine has patients with stories like this: *I can't catch my breath,* they tell the pulmonologist, but then the CT scans check out fine. *I have chest pain,* they tell the cardiologist, but their ECGs are all clear. *My stomach is killing me,* they tell the gastroenterologist, and yet imaging, endoscopy, and sometimes even surgery fail to turn up reasons why.

Patients with various kinds of psychosomatic illnesses can seem "kind of like the same person," says David Levinthal (PhD '04, MD '06, Fel '12). And often, they're "*literally* the same person who has symptoms across multiple body systems." Levinthal directs UPMC's Neurogastroenterology and Motility Center, a tertiary-care clinic where patients go when neither their primary care physician nor a community gastroenterologist has been able to help. Plenty of referrals for severe, unexplainable, intractable irritable bowel syndrome come to his door. And typically, GI symptoms aren't all these patients are dealing with. Panic attacks, depression, and early life trauma are all over their charts. So are meds for chronic pain, meds for high blood pressure, meds for fast heart rate, and more.

ARTWORK | GREG DUNN

So if all of the standard test results are normal, asks Levinthal, "What's more likely? That you have 10 things independently wrong with you, or that the master regulator is off?" That master regulator being the neural network that governs organ function. Or, in an another way of putting it which these patients hear way too often: *It's all in your head.*

"Well, it *is* all in your head—because your brain is in your head," says Peter Strick, Levinthal's scientific mentor and collaborator. Ultimately, this network answers to one command-central, the brain.

Strick is the Thomas Detre Professor, chair of neurobiology, and scientific director of the Brain Institute (among other titles) at the University of Pittsburgh. A decade ago, he and Levinthal got together over a shared curiosity about the intersection of the mind and the body and tackled the problem from a perspective that's been largely missing from this field. Rather than focusing on more downstream measures of brain-body interactions (like hormone levels), they sought out the neural connections themselves. In August, their efforts culminated when Strick, Levinthal, and Strick's longtime collaborator Richard Dum, a research associate professor of neurobiology, published in *Proceedings of the National Academy of Sciences* (*PNAS*) a study that cuts to the crux of a paradox in modern medicine:

We all accept that stress is terrible for us, and that when our mental health suffers, the rest of our health follows suit. And yet the branch of medicine that's devoted to this integral relationship—psychosomatic medicine—is often written off as pseudoscience. The actual anatomical "connection" part of the mind-body connection was unknown.

In this study, the Pitt team became the first to map the elusive networks that connect an internal organ all the way to the brain. The researchers say the adrenal gland (specifically, the region therein known as the adrenal medulla, which is central to the fight-or-flight reaction), is the first of many internal organs that they plan to trace, a prospect that offers hope for broadening our understanding of how the brain influences the rest of the body.

And in this first paper, they've made unexpected discoveries about the inverse: how the body (or rather, certain muscles therein) can be used to influence the brain.

They found brain regions, hardwired directly to the adrenal medulla, involved in core-muscle movement—a finding that offers a possible explanation for why activities that focus on engaging these muscles, like yoga and Pilates, are said to be such stress relievers. (By the way, they knew it was the core muscles, specifically, because the movement aspect of the cortex covers "areas we've spent the last 30 years studying," says Dum. "We were the perfect people to do this.")

They also found circuits to brain regions involved in certain mood disorders—a new "stress-and-depression connectome," as Strick puts it. As these networks sharpen in focus, eventually it may be possible to intervene in mental illness right where it lives, in the wiring itself. "Deep brain stimulation is in major growth in neurosurgery" for a variety of diseases and disorders, notes Strick. He believes the new tools his team has developed offer hope for defining these multiple, distinct, yet interconnected networks at a level of detail that has never been possible before.

This new stress-and-depression connectome also includes a brain region that lights up in mindful meditation, adding to a list of findings that show the ancient practice actually does influence the brain. "It's only in the last 25 years that Western medicine has acknowledged, *Oh, those things have worked for people for thousands of years*," Levinthal says. "I think we just need to be open to the fact that, if done the right way, mind-body interventions could be just as valuable as everything else we do."

In his clinic, it all starts with listening—*lots* of listening. Then he explains that gut-churning agony doesn't always stem from the gut; often, it's a reaction to anxiety, depression, or some other poison of the psyche. (Remember, at this point, just about everything else has been ruled out.) Then, as he carefully takes the patient off the pills that have Band-Aided so many symptoms through the years, he works with the patient to confront the problem at its source.

"Amazingly," Levinthal says, "getting help for the mental health issues seems to make a huge impact on the GI symptoms."

In the Western world, prior to the 19th century, if you went to your doc with a complaint, his first thought would have been that something was amiss upstairs. His Rx: *Get thee to the beach.* Then medicine became more of a heads/entrails coin—germ theory taking over on the one side, and later, psychoanalysis and psychopharmaceuticals on the other. For the most part, the brain and body parted ways.

In college in the '60s, Strick was already curious about the brain-body bond. He did a summer research project for Barney Dlin, a famous physician-scientist in the field of psychosomatic illness. "It was always there in the back of my mind, the whole notion [that people think it's] imaginary," says Strick. "Just the name, *psychosomatic*, it's like calling somebody a psycho."

After his BA in biology and PhD in anatomy (both from the University of Pennsylvania), Strick worked for four years as a fellow in Edward V. Evarts's Laboratory of Neurophysiology at the National Institute of Mental Health, where Strick probed brain structure–function relationships and, in some cases, developed new techniques to do so. The dye-based tracing methods that were available at the time had big limitations—namely, when a tracer was injected into the brain, the tracer lost potency before passing any farther than the next neuron over. To get anywhere with this research, he realized, he would have to reveal networks in their entirety.

Through the '80s and '90s, at the VA Medical Center at Syracuse, N.Y., Strick honed the use of certain viruses, previously used to trace neural networks in rodents, for nonhuman primates. He started out with the cold-sore virus (herpes), then switched to rabies, because it moves very quickly. It travels along the central nervous system backwards, toward the brain, replicating from neuron to neuron in predictable 8- to 10-hour cycles. The path of the infection can be tagged with antibodies to reveal a clear road map.

Using this viral-tracing strategy, the Strick lab has uncovered previously unknown fundamental networks of movement—especially voluntary movement. His group also revealed a division of the cortex that's likely responsible for the uniquely human capacity for fine-motor movement, discovered the cerebellum as a potential new target for dystonia treatment, and uncovered previously unknown connections between brain regions, among many other high-profile findings. Strick, who joined


Strick


Levinthal


Dum

the University of Pittsburgh in 2000, is now a member of both the American Academy of Arts and Sciences and the National Academy of Sciences.

Levinthal is the son of a psychologist (his dad was chair at Hofstra University) and grandson of a human factors engineer for an aerospace company. Levinthal always knew he wanted to be a scientist, too. One of his very first school projects used biodots—little color-changing stickers that indicate skin-surface temperature—which 11-year-old Levinthal compared to his test subjects' reported emotional states throughout the day. Even as a fifth grader, he was getting at the idea "that how we think and feel and what we're doing matters for how our body is responding."

Levinthal came to Pitt for the Medical Scientist Training Program (MSTP)—a dual-degree track for physician-scientists—and completed his neuroscience PhD and his MD in 2004 and 2006, respectively. (The overachiever cofounded the Pittsburgh Center for Pain Research while he was still a med student.) Six months before he was bound for an internal medicine residency at the University of Michigan, he met Strick and in short order joined his lab. Levinthal was fascinated by the possibilities that viral tracing presented for his research interests in the cerebral-cortical processing of pain. They continued their collaboration long distance, publishing a 2009 paper on what's called the spinothalamic tract—a study that was "full of surprises," Strick says. (Ascending pain signals to the cortex, it turns out, seem to influence not only cognition and sensation, but also motor planning and execution.)

Levinthal returned as soon as he could, in 2008, as a GI fellow, eager to begin a project on the stomach. This work would later snag him a career development award from the National Institutes of Health. Though the paper is still in the works, Levinthal has already presented his findings at professional meetings.

At the same time, Strick was spearheading projects on other organs, starting with the adrenal medulla. (Remember: That's a subregion of the adrenal gland—not a part of the brain, much as it sounds like it should be to a layperson's ear.) In speculating which parts of the brain were the origins of the adrenal medulla's wiring, most neuroscientists figured that the cerebral cortex—that wrinkled, gray outer layer of the brain—had maybe one or two areas connecting to the organ. A highly developed cortex is one of those brain features that separates us from other animals—think higher-level stuff like controlling your emotions, fine-tuning your body movements, and so on. Fight or flight, on the other hand, is universal across vertebrates—so it is likely linked to deeper, old-brain sort of stuff, the thinking went.

The team conducted tracing studies, first in the rat and then in the nonhuman primate, eager to see what had changed in the course of evolution. And they were surprised by what they found: A whole mess of connections—several times more than those in the rat—many of which were in regions of the cortex that the rat didn't even have.

Though this finding was unexpected, it had a certain logic. When we humans get stressed out, we're capable of far more than merely throwing punches or high-tailing it out of there. We can make jokes, talk it over, hold our tongues.

The team was intrigued to learn that most of the cortical connections were plugged directly into the areas for movement planning and performance, especially the primary motor cortex region for the core—those deep, stabilizing muscles stemming from your spine and pelvic bone. Given this, it's no wonder people who do core exercises say they're so much happier for it, Strick says.

When you make even simple movements, like twisting a light bulb, there's plenty of stuff going on behind the scenes: adjusting your heart rate to maintain your blood-oxygen level, redistributing blood to muscles that need it—automatic functions that control your adrenal medulla, kidney, heart, and so on to keep you alive. We've long known that these housekeeping chores happen concurrently with voluntary movements, but we've never been sure how they fire together so precisely—there was no evidence that they were part of the same system, says Dum. The *PNAS* paper offered some explanation: "Top-down" signals are plugged not only into the system behind your voluntarily moving, lightbulb-twisting arm, but also into your autonomic nervous system, of which the "fight or flight" network is a part—and they appear to have overlapping circuitry after all.

**So if all of the test results are normal, asks Levinthal, "What's more likely? That you have 10 things independently wrong with you, or that the master regulator is off?"**

So perhaps, says Strick, if your core muscles are weak and have to strain with every move you make, the brain has to work harder to make them keep at it. And that hard work amounts to stress. (This is all speculation, he adds—he's eager to see others put his findings to the test.) And so, as Strick recently told *The Atlantic*: "My kids would tell me, 'Dad, you ought to take up Pilates. Do some yoga.' But I'd say, 'As far as I'm concerned, there's no scientific evidence that this is going to help me.'" Well, out of the mouths of babes. (His kids are grown, but you get the point.) Now he's found some evidence.

Second to the motor cortex, the brain areas with the most connections to the adrenal medulla were in a region known as the anterior cingulate cortex, or ACC. Which was fascinating, because the ACC is involved in our very thoughts and feelings—not old-brain stuff at all.

The ACC is part of what can be described



as our emotional and self-referential system—the machinery behind how we decide what events in our lives mean to us, says Tor Wager, a leading researcher in this field and director of the Cognitive and Affective Neuroscience Laboratory at the University of Colorado Boulder. In brain scans, you can see evidence that the self-referential system is altered in people affected by trauma, abuse, poverty, and neglect. It's also linked to chronic pain.

"I think this is a landmark paper," Wager says. "It provides a really solid physiological foundation for some of the relationships we're seeing with human fMRI of stress." Human imaging can be used to identify correlations with responses in the body, he says, "but this neurological tracing in the nonhuman primate is another level of detail. I'm really enthusiastic."

Fight or flight is essential. In the event of real danger, you need your adrenal medulla to kick in, widening your pupils to attention, pumping blood to muscles, and pausing digestion as you mobilize your energy stores to be ready for whatever comes next.

But a chronic state of all the above can be a damaging system overload, literally from the top down. And unfortunately, the Pitt team found, we are hardwired with a vulnerability to that overload: The ACC, that region so connected to the adrenal medulla, lights up even when we perceive a mild conflict, or beat ourselves up over a mistake, or reimagine what we regret from the past. Which means all of the body's potent stress-response effects are kick-starting, too. Hence, the team believes, post-traumatic stress disorder (PTSD)—a condition characterized by haunting flashbacks, nightmares, and survivor guilt—may well be a mix-up in this wiring. A person's pulse might shoot through the roof every time he thinks a certain thought, says Levinthal, because he's "essentially reliving the stress response from the initial inciting event and . . . getting stuck in this pattern."

One of the adrenal medulla–linked subregions they found in the ACC—the subgenual—has been implicated in the neuroanatomy of mood disorders, a subject that Helen Mayberg, professor of psychiatry, neurology, and radiology and the Dorothy Fuqua Chair in Psychiatric Neuroimaging and Therapeutics at Emory University, has been studying since the 1980s. Over that time she has drawn a map that was highly informed by Strick's work, in a kind of "collaboration by proxy," as she puts it. This map has enabled her to bring to clinical trials a new therapy that the field of psychiatry is abuzz over: deep brain stimulation for severe, intractable depression. "For people who are ill who basically have run out of options, it's another chance," she says.

There have always been clues that movement and depression are linked, Mayberg notes: Babies tense up and freeze when they cry, and young animals stay put when they're separated from their mothers. People with depression have a hunched posture to them,



**The team members also revealed a "stress-and-depression connectome," raising hope that mental illness may one day be treated at its source, in our wiring.**

as well as a sluggishness that, as the illness progresses, can devolve into a kind of "virtual paralysis."

But this relationship between depression and movement was unclear. Was an altered movement network the cause or the effect?

Mayberg's PET and fMRI scans show that depressed people have aberrations in their limbic-cortical networks (including the subgenual and pregenual ACC). This, along with corroborative evidence in the Strick lab's *PNAS* paper, has provided a new lead: "What we can see now," says Strick, "is cortical motor areas are really influencing regions involved in stress," to which depression is directly linked.

The other main ACC subregion Strick's team found in the stress-and-depression connectome—the pregenual ACC—is of particular interest for Wager, who throughout his career has been fascinated by how our thoughts and beliefs can affect health. The pregenual ACC, he explains, is among the areas that respond most reliably in his human brain-imaging studies of the placebo effect, a major area of focus in his lab. He says the Pitt team's paper "provides a firmer scientific foundation" for findings on placebo effects on the body.

The pregenual ACC has another claim to fame. In addition to its link to the placebo effect, it's also the region that lights up in mindful meditation. Strick has always been skeptical about this mind-realigning technique.

Well, not anymore.

It might sound a little "out there," but it's true: We are brilliant, electrified beings. Our neurons are live-wired together in stunningly complex arrangements. Electrical signals shift into chemical signals and back again, crossing from synapse to synapse every moment we're alive. That is the basis of everything we think and feel and do, and it does not end at our necks; it continues all the way down through our beating hearts and churning guts and into the extremities that ground us.

Many drugs in common use target only the chemistry parts of this spark-chemical-spark chain. And drugs don't just patch our faulty circuits; they affect the entire machine. Hence your blood-pressure pills disrupt your digestion, and your bipolar meds put you to sleep in your chair.

If we had a clear road map for the wiring within us, it could change how doctors diagnose, treat, and measure progress in patients.

The Strick lab aims to draft that map—from head to toe, from childhood development all the way through the aging process—as well as this map's many perplexing variations. How does it change as we acquire knowledge and experience? And how is it altered in trauma? In cerebral palsy? Or in addiction?

Besides the ACC, the Pitt team also found a separate adrenal medulla–influencing system beneath the cortex, mainly in the basal ganglia—a site involved in reward processing and addiction. There's evidence that people caught in the damaging cycle of substance use have actually formed new connections in their brains, Strick notes. "This puts a whole new perspective on it. It's a brain-based approach." Those 12-step programs, unfortunately, don't work for everyone—only 5 to 10 percent. "For those people, it's fantastic," he says, so what is it about their brains and connections that makes that effective?

Picture a world where we could know the distinguishing features of a particular person's case of alcoholism, or PTSD, or IBS, or chronic pain. Brain structure–function correlates could be charted as patients progress—or fail to—and a careful study of the patterns that emerge could give rise to subtypes within each of these illnesses. Perhaps one day, doctors could look at your brain scan and instantly know, for example, how likely cognitive behavioral therapy, or deep brain stimulation, or a particular pill would be of help. (Mayberg has already published on exactly this.) Or maybe your doc could even tell you what you—given your genetic susceptibilities, or traumatic childhood, or adrenaline-fueled job—can do to minimize your chances of ever getting sick in the first place.

"You're talking about personalized medicine," says Strick.

In the clinic, Levinthal sees plenty of people who've been stuck in a loop of doctors' appointments for decades, with lengthy lists of diagnoses and misdiagnoses in between. And while undoing such deeply ingrained brain-to-body circuits isn't something patients can accomplish overnight, there's heartening news: The successful path to therapy may be something they can actually gain some control over.

Levinthal's favorite scenario is when he first meets a patient as a college student. A snarl of stress and indigestion, the kid shakes his hand and tells him her story. And then the GI doc gives his pitch:

*It's okay. You're just the kind of person whose body does this when you're stressed out. I want you to learn how to not do that. And you can learn. If you invest now in these coping skills, your life path is going to be awesome.*

"And often," says Levinthal, "it's just a few visits, and they're feeling better." ■

*Editor's note: This is the first of a two-part series on brain-body biology.*