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Hemispheres of Influence: Bridging the Disconnect between Environmental Neurotoxicology and Clinical Practice

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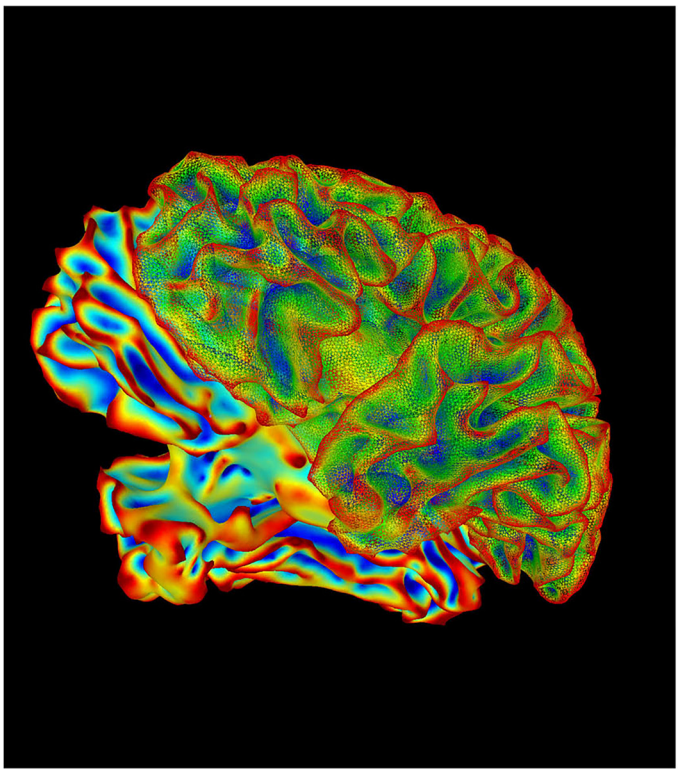
William Mack runs a translational science laboratory focused on inflammation and oxidative stress. Years ago, this interest led him on a path toward investigating inflammatory effects of airborne particulate matter, which are increasingly recognized as risk factors for stroke and neurological disorders.[1,2] Mack, a neurosurgeon at the University of Southern California's Keck School of Medicine, was soon working with neurotoxicologists and environmental health scientists–collaborations that are fundamental to his research, he says. But as someone who integrates neurotoxicology with his own clinically based investigations, Mack is in rarified company.

Despite growing evidence connecting chemical exposures with a range of neurological diseases, the fields of environmental health and clinical neuroscience "exist in parallel with almost no bridging between them," says Deborah A. Cory-Slechta, a professor of environmental medicine and pediatrics at the University of Rochester Medical Center. Samuel Goldman, a professor of clinical medicine at the University of California, San Francisco, agrees. "Everyone pays lip service to the idea that neurological diseases can arise from some combination of genetic and environmental factors, he says. "But that is usually about as far as it goes."

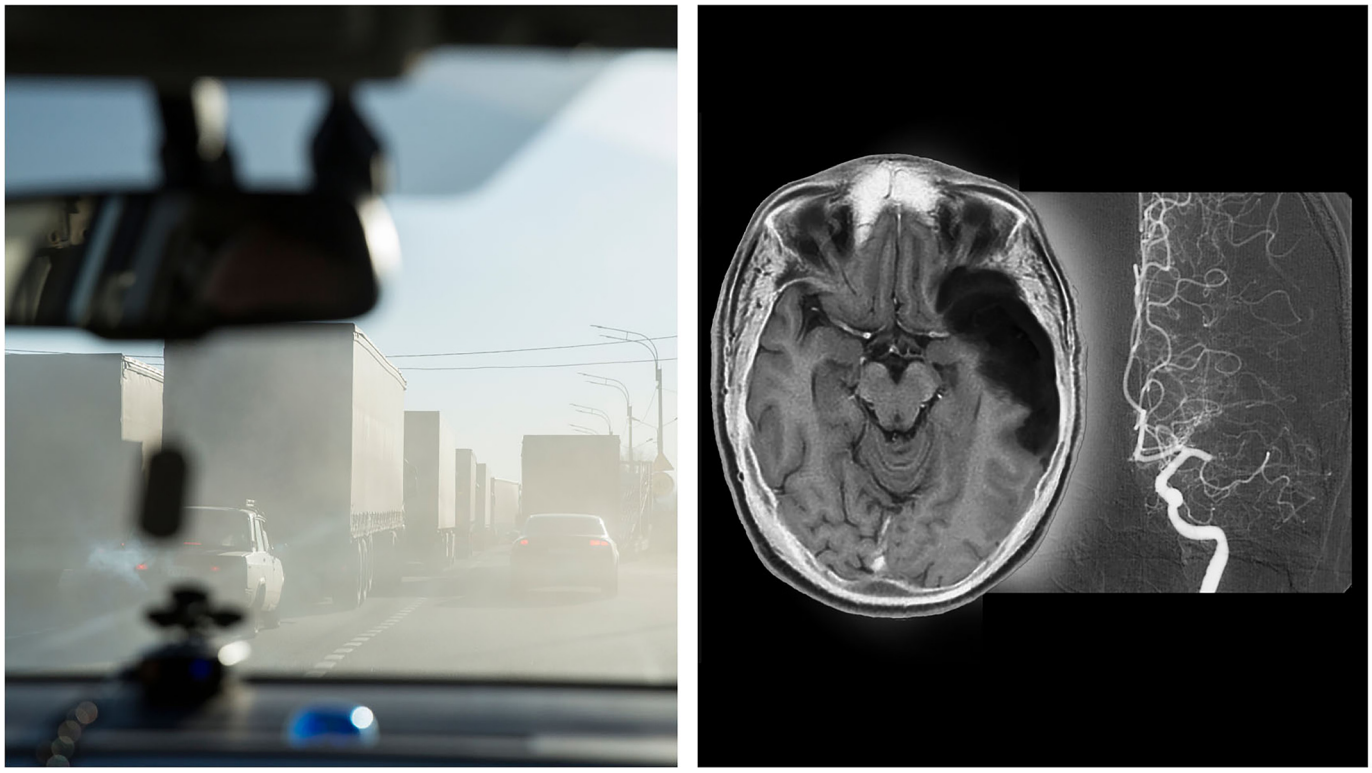
That disconnect has real-world implications: If scientists are unable to ascribe clear or even suspected roles for environmental exposures in a given disease, then clinicians can provide little evidence-based advice for patients about environmental risk factors, says Heather Volk, an associate professor of mental health at the Johns Hopkins Bloomberg School of Public Health. In return, clinicians do not share with investigators real-world insights that might help point environmental health research in new directions. Volk adds that if we can do a better job connecting population-level exposures to therapeutic opportunities, "then we can converge on evidence and pathways that allow us to move toward preventative policy changes or improvements in standards of care."

Unrivaled Complexity

The inaccessibility of brain tissue and the complexity of the brain's underlying biology and associated behaviors have traditionally made it difficult to bridge gaps between neurotoxicology and clinical neuroscience. Marc Weisskopf, a professor of environmental epidemiology and physiology at the Harvard T.H. Chan School of Public Health, points out that human and animal brains contain a greater variety of cell types than other organs. Our knowledge of how these different cell types work together to produce a given behavior is, he says, much less advanced than our understanding of how heart cells, for instance, coordinate to produce a particular rhythm.



The disconnect between environmental toxicologists and clinicians has real-world implications for people's health, and there is growing recognition among neuroscientists that many neurological disease cases cannot be explained by genetics alone, says investigator Pamela Lein. (Right: Rendering of a human brain created with software called SUMA using functional magnetic resonance imaging data.) Images, left to right: © iStockphoto/SolStock; National Institute of Mental Health, National Institutes of Health.



Experiments using rodent models are yielding evidence of how exposure to particulate matter may affect stroke risk in humans. (Right: MRI images from a middle-aged woman who has had a stroke. The black area of the brain image shows where the stroke occurred; the bright white line is the carotid artery on the same side of the brain.) Images, left to right: © IvSky/Shutterstock.com; © ZEPHYR/Science Source.

A further complication is that animal and human brains differ significantly with respect to the timing of gene expression and the functionality and profiles of resulting proteins, according to Pamela Lein, a neurotoxicologist at the University of California, Davis. For instance, a protein expressed by a single gene in the human brain may be expressed by multiple genes in the brain of a zebrafish, she explains. Genes in certain species can have multiple functions that, in turn, confound efforts to translate results from experimental assays into relevance for human health.

Analogous problems arise for scientists attempting to use animal models to study the behavioral symptoms of conditions such as autism or attention deficit/hyperactivity disorder. "We know that behaviors are disrupted in kids with autism, but how do you measure the corresponding behaviors in animals?" Lein asks. "We can look at social behaviors in rodents and ask whether they correlate with what we see in humans. The tools we have for doing that are getting better and more sophisticated, but there isn't a perfect overlap."

To Jean Harry, the neurotoxicology group leader in the Mechanistic Toxicology Branch of the National Institute of Environmental Health Sciences (NIEHS) Division of the National Toxicology Program, these issues underscore a fundamental challenge. "It's still very difficult to experimentally model a human [neurological] disease, and thus, many of the selected end points—whether from human epidemiology or laboratory studies—provide only screening-type data and show associations rather than causal relationships," she says. "We can model aspects of the disease to study the underlying biology, but—apart from poisonings—when you try to link the environmental exposure to a human disease process, things start to fall apart."

This difficulty in modeling neurological disease is also why clinical neuroscientists tend to reject evidence of toxic effects that is derived solely from *in vitro* assays or animal tests, Lein says: "You typically need evidence in humans before you get buy-in." To collect that evidence, investigators are developing new animal models that better reflect human exposures and potential health effects.

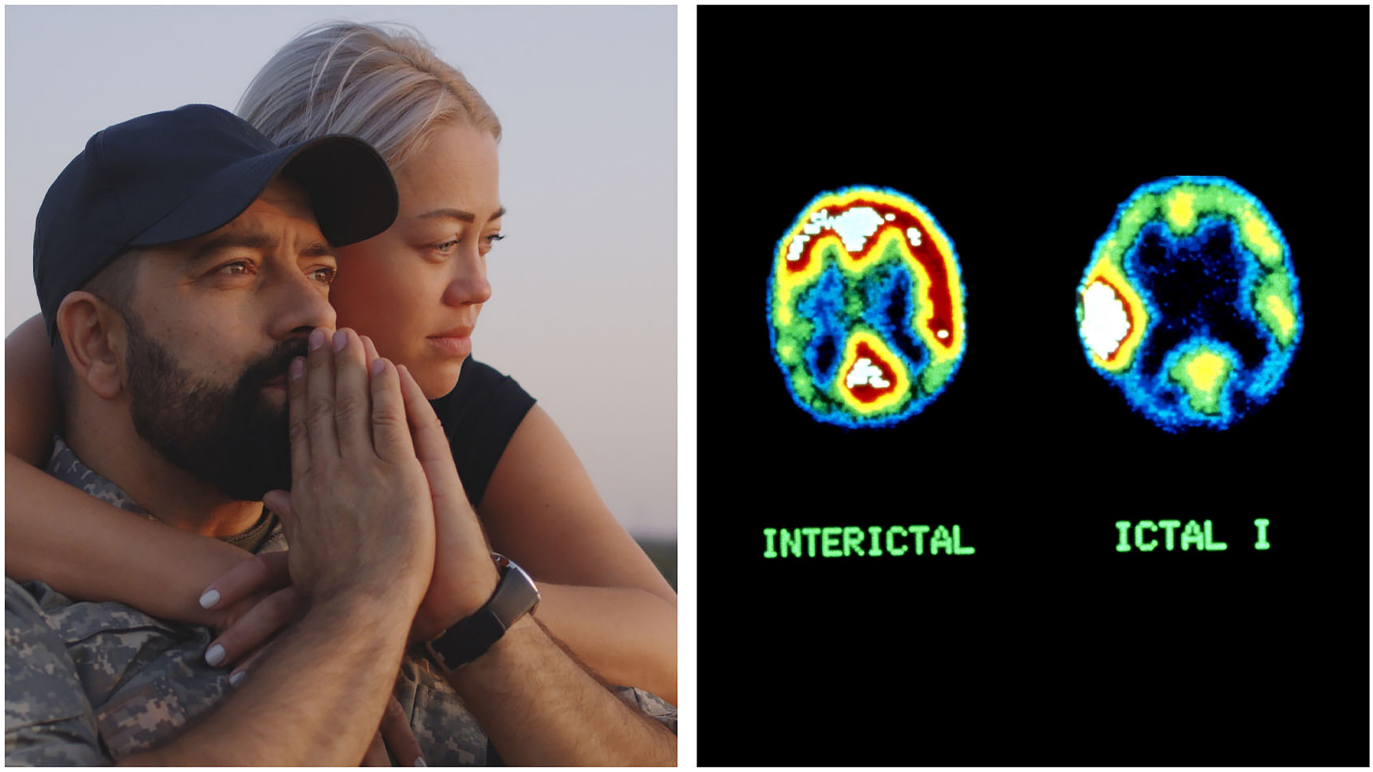
Integrating the Fields with Magnetic Resonance Imaging

One way to begin integrating the fields, Weisskopf says, is to measure experimental end points in animals that correspond as closely as possible to a human condition. Recent advances in magnetic resonance imaging (MRI) are proving especially useful along those lines.

MRI uses a large magnet, radio wave transmitter, and computer software to construct detailed images of structures in the body.[3] The technology is becoming more powerful, with high-resolution instruments able to image dynamic processes and fine anatomical details in the brain.[3] According to Mack, MRI can image pollution effects on blood vessels ranging from large arteries to the tiniest capillaries that interface with the brain's white matter.

Mack's team uses the technology to study how brain changes in stroke patients living in parts of Southern California with high air pollution compare with changes in the brains of laboratory rodents exposed to nanoscale particulate matter (nPM). During one study,[4] the researchers induced stroke in laboratory mice after first exposing the animals to nPM. They found that nPM produced neuroinflammatory effects that primed the animals for worse stroke symptoms, compared with unexposed mice. More recently, Mack's team found that nPM exposure altered working memory in a mouse model of carotid artery disease; however, exposure did not affect working memory in healthy mice.[5]

"These are the types of outcomes we can look for in patients," Mack says. "We think exposure to particulate matter may cause



High OP exposures like those during a chemical attack can cause seizures and long-term neurological abnormalities. Researchers are using a rodent model of OP poisoning to assess possible mechanisms. (Right: PET images of the same brain showing normal activity on the left and seizure activity on the right.) Images, left to right: © iStockphoto/EvgeniyShkolenko; © SCIENCE SOURCE/SCIENCE PHOTO LIBRARY.

small blood vessels near the stroke site to occlude more easily. These vessels typically help provide blood flow and oxygen to the area of the brain that is affected by the large vessel blockage from the stroke."

Despite its advantages, MRI usefulness is hampered by the slowness with which structural effects from pollutant exposures become apparent—sometimes taking years. Fortunately, another technology, positron emission tomography (PET), detects biochemical responses almost immediately. "It's an indicator of active brain chemistry," says Tomás Guilarte, a professor in the Department of Environmental Health Sciences at Florida International University.

PET Scanning: Another Bridge Builder

To perform a PET scan,[6] researchers first inject a minimally radioactive tracer ("radioligand") that travels through the bloodstream and into the brain. A radioligand can be designed to bind a specific cell surface receptor. The PET scanning technology will then track the radioligand's position and provide a three-dimensional view of brain functioning. Guilarte says the technology allows researchers to evaluate a range of different neural systems and processes *in vivo*.

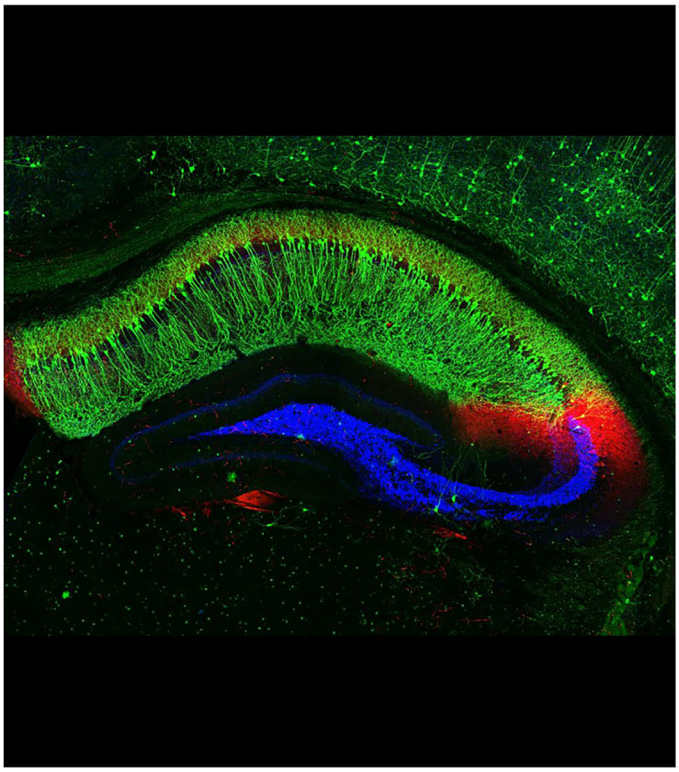
During his research, Guilarte used PET to overturn a prevailing view on the mechanisms underlying manganese-induced parkinsonism, a condition that produces symptoms similar to those seen in Parkinson's disease, including tremors, slow movements, and impaired speech.[7] Researchers previously thought that manganese triggers these symptoms by killing brain cells that release dopamine, a neurotransmitter.[8,9] Guilarte's investigations[10,11] using PET in nonhuman primates suggested that may be only part of the story. Manganese may also impair neurons' ability to release dopamine, he says; in other words, the affected cells survive but cease to function normally.[12]

Follow-up research with a mouse model of manganese-induced Parkinson's disease validated these findings.[13] In brain regions where manganese levels were highly elevated, Guilarte's team found that dopamine release was inhibited, even though the dopaminergic neurons themselves showed no evidence of degeneration.

For her part, Lein uses PET to study how acute toxic effects of organophosphate (OP) exposure can progress toward long-term complications. She has also used MRI to show that acute intoxication with the OP agent diisopropylfluorophosphate (DFP) produces structural changes in the brains of exposed rats that are similar to features seen in the brains of people with epilepsy.[14] Acute high-level OP exposures like those during nerve agent attacks or suicide attempts can cause status epilepticus (continuous seizure activity) and death.[14] Survivors of OP poisoning sometimes experience persistent cognitive impairments, affective disorders, and abnormal brain activity.[15,16] The question, Lein says, is what drives those changes.

To investigate, she and her team developed a rodent model of acute DFP intoxication.[17] The aim with this model, she says, "is to define a clinical profile in the rat that can be translated to humans to predict which people are at higher risk for developing long-term neurological consequences from acute organophosphate exposure." Ideally, insights gleaned from the model will inform new therapeutic strategies to ward off future neurological problems.

The investigators used PET to study neuroinflammatory changes in the rodents' brains at varying time points following exposure.[17,18] They used a radioligand that binds to translocator protein (TSPO), which is a validated biomarker of brain injury and neuroinflammation identified previously in Guilarte's lab.[19–21] TSPO is expressed by glial cells that support and protect the neurons that produce electrical impulses.[22] Glial cells are activated in response to injury,[23] and because TSPO expression increases in



Animal models are an imperfect surrogate for human behavior, to say the least. Molecular data may help close the gap. Growing evidence suggests that abnormalities in hippocampal zone Ca2 may contribute to social impairment in both humans and animals.[30] (Right: Confocal microscopy image of a mouse hippocampus showing zone Ca2 in red.) Images, left to right: © iStockphoto/Aleksandar Jankovic; Courtesy of Raunak Basu, University of Utah, Salt Lake City, with funding from the National Institute of Mental Health, under CC-BY-NC-2.0.

tandem, Lein can see specifically where neuroinflammation—and, potentially, neuronal damage—has occurred. So far, Lein's team has found evidence that, although neuroinflammation persists well after DFP exposure has ended, it does not appear to be the causative agent in the observed cognitive effects.[17,18]

Getting to *in Vivo*

Aligning experimental rodent data with end points for conditions such as autism or attention deficit/hyperactivity disorder is trickier, given that explanations for these complex behaviors are still quite rudimentary, Weisskopf says. "We still don't have a detailed enough understanding of the brain to know exactly what produces [less common] behaviors... for such disorders," he says. Still, some behavioral tests are showing promise.

Weisskopf singles out the acoustic startle test, which assesses a reactionary contraction of facial and skeletal muscles that occurs in reaction to a sudden stimulus, such as a loud noise. Because the basic brain circuits behind the reflex are conserved among different species, including humans, the test "provides a way to assess brain function according to a mechanism that's shared by animals and people alike," Weisskopf says. In one study, children with autistic-like traits reacted differently during a startle response test than children without such traits—their responses to weaker stimuli were more intense and longer-lasting.[24]

Weisskopf says researchers can also evaluate abnormalities in the context of chemical exposures, although he cautions that the acoustic startle test evaluates just one reflex out of a broad array of brain behaviors. "It's a peek into one little window of the brain," he says. "But it's directly translatable."

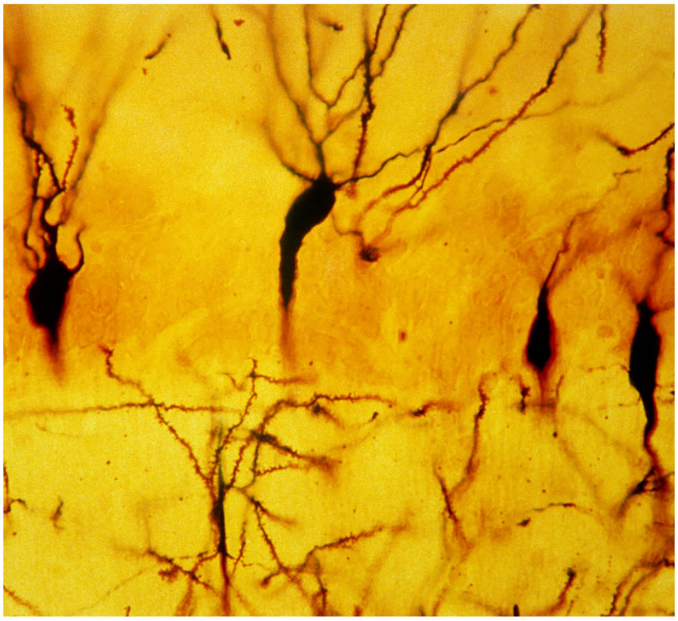
As the use of these approaches broadens, Lein says the gap between researchers in environmental health and clinical neuroscience could narrow further. Newer technologies—such as those focused on microRNA, transcriptomics, metabolomics, and the exposome—are bringing integration closer. Using molecular data, "we can correct for how modeling results differ from the *in vivo* situation," Lein says. Also helping to integrate the fields, she adds, is growing recognition among neuroscientists that many neurological disease cases cannot be explained by genetics alone.

Still, translating environmental evidence into clinical management poses difficult challenges. For instance, clinicians might view minor declines in intelligence quotient from lead exposure as inconsequential for an individual child, even though similar shifts affecting thousands of children on a population basis are worrisome to environmental health researchers.[25]

Connecting Exposures to Therapeutic Opportunities

Another complication is that, apart from a few persistent toxicants, chemicals implicated in neurological disorders may not be readily detectible in people's bodies, especially if the exposures happened in the past. "There are probably hundreds of studies associating pesticides with Parkinson's disease," explains Goldman, of the University of California, San Francisco. "However, identifying the specific agent that might have caused Parkinson's disease in a given patient is difficult, and most people have no idea what they were exposed to."

Furthermore, doctors are generally limited in their ability to test for prior exposure to environmental chemicals during clinical workups on patients, adds Avindra Nath, a neurologist and intramural clinical director at the National Institute of Neurological Disorders and Stroke. "I can order tests for heavy metals, but when it comes to other chemicals, we don't have standardized assays," he says.

Chemical exposures can cause neurological disorders that develop long after exposure ends, making it difficult to connect the two. (Right: Light micrograph of nerve cells in the hippocampus.) Images, left to right: © iStockphoto/Viktoria Hrekova; © BSIP, SERCOMI/SCIENCE PHOTO LIBRARY.

That said, "clinicians need to get over thinking everything is a disease," Harry says. She cites the example of kerosene fumes, which cause central nervous system toxicity and symptoms that include headache, dizziness, and unsteady gait.[26] "Doctors need more training about exposure-related effects that cause symptoms unrelated to disease processes," she says. For decades health care providers have been encouraged to take their patients' environmental health histories,[27] but evidence suggests this practice is not widespread.[28]

Closer integration of the fields, Harry adds, could provide benefits such as shared knowledge that helps patients and added insights from the clinicians who see them. "Clinicians have known for decades that some neurodegenerative disorders cause smell and taste impairments," Harry says, illustrating her point. "But this was a comparatively new revelation for epidemiology."

Cory-Slechta emphasizes that most neurodegenerative disorders arise from multiple risk factors, not just one. Stronger links between neuroscience and environmental health, she says, could allow for improved animal models that incorporate both chemical and nonchemical stressors, as well as better simulations of human environments and conditions.

Along these lines, a new Environmental Neuroscience Working Group, formed by the National Institutes of Health, recently requested public input on ways to promote interdisciplinary research between neuroscience and environmental toxicology.[29] The working group is co-led by David Jett, a neurotoxicologist and program director at the National Institute of Neurological Diseases and Stroke, and Cindy Lawler, chief of the Genes, Environment, and Health Branch in the NIEHS Division of Extramural Research and Training. The comment period ended 7 May 2022.

Jett says multidisciplinary research will benefit from rapidly growing data sources. "The large human cohort studies are all gathering exposure data," he says. "We have wearable and atmospheric sensors and geospatial data, and the number of biobanks is exploding." He also says that clinically oriented scientists who work on specific diseases increasingly recognize the importance of those environmental health data, adding that "I can't think of a better time for these collaborations to happen."

Charles W. Schmidt, MS, is an award-winning journalist in Portland, Maine, whose work has also appeared in *Scientific American*, *Nature*, *Science*, *Discover Magazine*, *Undark*, the *Washington Post*, and many other publications.

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