NEWS FEATURE

How air pollution threatens brain health

Long thought to primarily harm the lungs and cardiovascular system, air pollution is now catching the attention of neuroscientists and toxicologists.

Lynne Peeples, *Science Writer*

The buzz of a leaf blower and its gaseous fumes fill the air outside a lab facility at the University of Washington in Seattle. Inside the building, neurotoxicologist Lucio Costa is investigating how polluted air—such as garden tool exhaust—could be bad for the brain.

Next to the building sits a 5,500-watt diesel generator, enclosed in a metal box. Pipes carry the diesel exhaust—the same stuff emitted by diesel engines in vehicles and heavy equipment—into the facility, across an exposed ceiling and into a room where plastic cages of mice are stacked high against the wall. Tubes filter the diesel exhaust through the cages, Costa explains, in an effort to mimic the contaminated air you might breathe while sitting in traffic or living near a busy road.

After spending most of his career studying mercury, pesticides, and flame retardants, Costa knows well that many toxins in the environment can hurt the brain. But only in the last several years has the possibility of air pollution as a culprit crossed his mind. A growing body of literature on the topic inspired him to begin research in this diesel lab. "For a long time, I thought that air pollution was affecting mostly the lungs and the cardiovascular system and not the brain," says Costa. "So I stayed away from any issue related to air pollution."

Now, mounting evidence seems to link a variety of neurological problems to dirty air. Troubling recent findings include hallmarks of Alzheimer's disease

Although stay-at-home orders have provided some respite from major pollution in cities such as Delhi, India, overall pollution increases may be causing not only cardiovascular problems but cognitive decline. Image credit: Shutterstock/Saurav022.

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found in the brains of children living in Mexico City (1) and a nearly doubled risk of dementias for older women in highly polluted parts of the United States (2). Costa's own research has identified autism-like social and behavioral issues in mice exposed to diesel exhaust (3). Today, Costa is among a growing cadre of biologists, toxicologists, and doctors raising the alarm over this pervasive yet overlooked menace to our memory, attention, and behavior.

A Global Threat

Although the coronavirus disease 2019 (COVID-19) pandemic and associated "shelter in place" policies have reduced fossil fuel use to offer a temporary respite from extreme pollution in some places, most countries face an ongoing epidemic of dirty air as a result of growing urban congestion and an uptick in climate-driven wildfires, among other factors. Indoor air pollution further plagues many of the world's poorest communities. Around 3 billion people cook indoors over open fires or stoves fueled by wood, biomass, kerosene, or coal. In 2018, the World Health Organization (WHO) identified air pollution as the second-largest risk factor for noncommunicable disease worldwide. And the WHO's stats don't include the full range of neurological effects now being discovered, notes neurotoxicologist Deborah Cory-Slechta at the University of Rochester in New York.

Globally, more than 90 percent of people breathe air that fails to meet WHO standards. That includes an estimated four in 10 people in the United States, although efforts such as the US Clean Air Act and its amendments of 1990 have helped. Between 2000 and 2016, the average concentration of particulate matter (PM) with a diameter of less than 2.5 micrometers (PM2.5), tiny particles produced by combustion, fell by around 40 percent in the United States. But the country's overall air quality has worsened since 2016. Partly to blame is a rise in wildfire smoke, which is now responsible for an estimated 40 percent of particulate matter pollution.

Yet cleaner, healthier air remains achievable, notes Dean Schraufnagel, a pulmonologist at the University of Illinois at Chicago. "There are no death certificates that say air pollution exposure," he says. "But we know that air pollution affects every organ in the body. If we stop the air pollution at its source, we can get strikingly important health benefits."

Schraufnagel, also the director of the Forum of International Respiratory Societies, points to one easy target: idling diesel-powered school buses. A 2019 study out of Georgia in the United States found that districts that retrofitted school buses to reduce diesel emissions reported significant increases in students' English test scores as well as smaller improvements in math (4).

The havoc air pollution can wreak on the brain is also a new area of interest for Schraufnagel, whose research and clinical practice has long focused on lung disease. Today, he is working with international organizations to get air pollution on the minds of not just pulmonologists but also neurologists and other medical experts. "This should be a call to action," adds Schraufnagel.

Size Matters

Air pollution is a cocktail of suspended gases, solids, and liquid particles. While this mix contains numerous hazardous ingredients, such as ozone, sulfur dioxide, and carbon monoxide, the component that appears most concerning for the brain is PM.

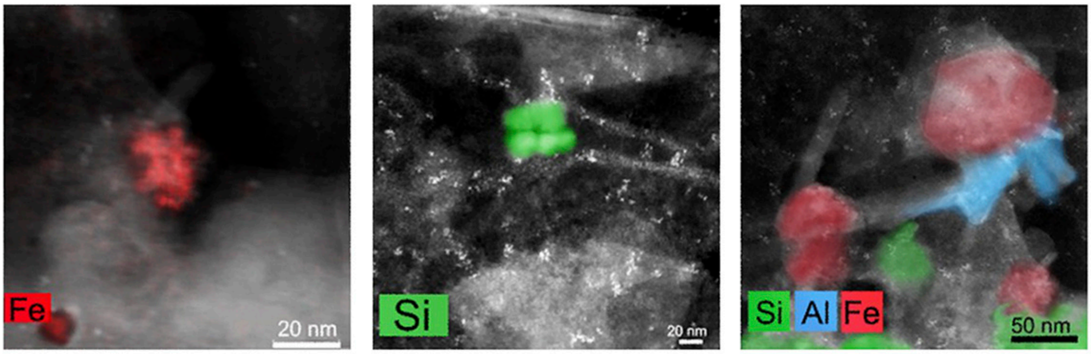
The US Environmental Protection Agency (EPA) regulates PM10 and PM2.5, defined as particles less than 10 and 2.5 micrometers in diameter, respectively. PM2.5, also known as fine particulate matter, generally comes from smoke, dust, and vehicle exhaust. Because PM2.5 is so tiny—30 times smaller than the width of the average human hair—it can remain airborne for long periods of time, infiltrate buildings, and penetrate the body. Ultrafine particles, which measure less than 0.1 micrometer across, may be even worse offenders. Yet the miniscule mass of these particles makes them difficult to monitor. They remain unregulated by the EPA.

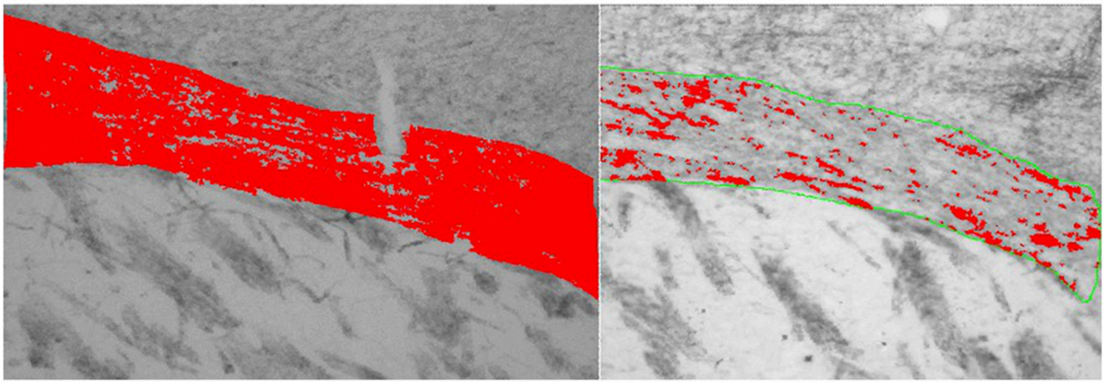
Fine and ultrafine particulate matter tends to circumvent the mechanisms that the human body has evolved to deflect, detain, and destroy unwelcome visitors. "The health effects of air pollution are all about particle size," says Cory-Slechta. Studies suggest that these tiny particles can even go up the nose and be carried straight to the brain via the olfactory nerve (5)—hence bypassing the blood–brain barrier. And they don't travel alone. On their surfaces these particles carry contaminants, from dioxins and other chemical compounds to metals such as iron and lead. "PM is simply acting as a vector," says Masashi Kitazawa, a molecular neuropathologist at the University of California, Irvine. "It might be a number of chemicals that get into the brain and act in different ways to cause damage."

Because of their large surface area relative to their volume, the smallest particles are the biggest offenders. Cory-Slechta's research has largely focused on lead and mercury, neurotoxic metals that are abundant in air pollution. "Ultrafine particles are like little Trojan horses," she says. "Pretty much every metal known to humans is on these."

Metal-toting particles that reach the brain can directly damage neurons. Both the particles themselves and their toxic hitchhikers can also cause widespread harm by dysregulating the activation of microglia, the immune cells in the brain. Microglia may mistake the intruders for pathogens, releasing chemicals to try to kill them. Those chemicals can accumulate and trigger inflammation. And chronic inflammation in the brain has been implicated in neurodegeneration (6).

Particles may also afflict the brain via the bloodstream. Research shows that small particles can slip through the plasma membrane of alveoli—the tiny air sacs in the lungs—and get picked up by capillaries. The particles are then distributed around the body in the blood. Although some of these particles may eventually breach the blood–brain barrier, a pollutant need not enter the brain to cause trouble there. The





After 14 days of exposure to pollutants during the gestational period, researchers found deposits of trace elements silica (Si), iron (Fe), and aluminum (Al) in rat brains (*Top Right*). They also found a loss of myelin—the insulating sheath around nerve fibers—in the corpus callosum of male rat brains (*Bottom Right*). Image credit: Uschi M. Graham (University of Kentucky, Lexington, KY) (*Top*) and Deborah Cory-Slechta (*Bottom*).

immune system can react to particles in the lung or bloodstream, too, triggering widespread inflammation that affects the brain.

Even an ingested particle could have indirect neurological effects, via the gut. Researchers now recognize strong connections between the gut microbiome and the brain (7), and studies show that delivering fine particles to the gut can cause systemic inflammation (8).

A Toxic Turn

In January 2010, Cory-Slechta received a surprising request from some University of Rochester environmental medicine colleagues. Typically, the group researched the effects of air pollution on the lungs and hearts of adult animals. But they had just exposed a group of newborn mice and asked Cory-Slechta's team to look at the brains.

At first she didn't think much of the request. Cory-Slechta was much more concerned about deadly lead exposure in children, her research focus at the time. "I didn't think of air pollution as a big problem for the brain," she says. Then she examined the animals' tissue. "It was eye-opening. I couldn't find a brain region that didn't have some kind of inflammation."

Her team followed up with their own studies. In addition to inflammation, they saw classic behavioral and biochemical features of autism, attention-deficit disorder, and schizophrenia in mice exposed to pollutants during the first days after birth. The mouse brains had noticeably less white matter, particularly in the corpus callosum connecting the right and left cerebral hemispheres. In work published last November, Cory-Slechta's group further linked short-term exposures to air pollution with impaired learning and memory in aged mice, based on measures of spontaneous movement, navigation of a maze, short-term object recognition, and the ability to discriminate odors (9). The concentrations of particulate matter used, she notes, "easily include sitting in traffic in major cities."

The work adds to a mounting literature on air pollution's unanticipated effects on the brain. Some of the first data came from Mexico City in the early 2000s, shortly after the United Nations declared it the most polluted city on Earth. Those studies identified signs of DNA damage, inflammation, degradation of the blood–brain barrier, and Alzheimer's-type pathology in stray dogs living in the city (10, 11).

But many researchers were initially skeptical. Such observational studies could not prove that air pollution caused the neurological changes. Urban dogs encounter many stresses, such as traffic noise, that may correlate with air pollution. For people, potential confounders include access to green space and a range of socioeconomic factors. "To be honest, I didn't believe in the studies," says Amedeo D'Angiulli, a neuroscientist at Carleton University in Ottawa, Ontario, Canada. He adds that he didn't *want* to believe them: The implications were too frightening.

D'Angiulli later ran into the lead author of those studies, Lilian Calderón-Garcidueñas, at a conference. They then began corresponding via email and she suggested he analyze the data himself. D'Angiulli did. And after he uncovered the same patterns, the two started collaborating on research that not only replicated the previous canine observations, D'Angiulli says, but also suggested that it was more than dogs that were in trouble.

Based on MRI scans, cognitive tests, and measures of inflammatory markers in the blood, the team identified neuroinflammation, brain structure changes, cognitive deficits, and Alzheimer's-like pathologies in apparently healthy children living in Mexico City, compared with a group of similar children in a less polluted city. The findings, according to the authors, suggested that dirty air may spur brain disease at far younger ages than previously suspected (12). In a 2018 study, Calderón-Garcidueñas, now a toxicologist at the University of Montana in Missoula, found above-normal levels of both amyloid and tau proteins in more than 99 percent of autopsies conducted on 203 city residents—one just 11 months old.

Other epidemiological studies have strengthened the connection by looking at the relationship between the exposure dose and the resulting risk. Research in Ontario, Canada, found that living farther away from a major road lowered the risk of developing dementia (13). A study of nearly 3,000 Barcelona schoolchildren found that those attending schools with more traffic pollution had slower cognitive development (14). And in the United States, a study found that living in locations where ambient particulate matter exceeded EPA recommendations nearly doubled women's risk of developing dementia. When those researchers looked specifically at older women with two copies of the *APOE4* gene variant, a strong genetic factor for Alzheimer's disease, the dementia risk associated with living in those locations jumped almost threefold (2).

Catching Air

Still, controlled studies in animals provide some of the strongest and most detailed evidence of air pollution's impacts. Many of these studies use ambient air from polluted environments to simulate real-world exposure—researchers are gathering air particles near roadways, harbors, oil refineries, and traffic tunnels.

Pamela Lein took the unusual step of bringing her research animals to the source. The molecular biologist at the University of California, Davis, recently spent two years converting a single-wide trailer into a vivarium that now sits adjacent to a traffic tunnel in northern California.

A system of ducts pulls air from the tunnel directly into the trailer, which holds 216 rodent cages. Some of the animals in Lein's studies receive air straight from the tunnel to experience daily and seasonal fluctuations in gases and particulate matter, along with the traffic vibrations and noise. Another group of animals breathes filtered, clean air but is exposed to the same vibration and noise, while a third group—back at a lab on campus—gets clean air, peace, and quiet. The arrangement allows the researchers to separate any potential effects of vibration and noise from those of the pollution as they look for effects on the brain and behavior over several months.

Although Lein's findings are not yet published, she reports "remarkable changes" in the brains of rat pups exposed to traffic-related air pollution throughout gestation and nursing, including an excess of new neurons forming in the developing brain. (Too many neurons can be just as detrimental to brain function as too few, she notes.) After lifelong exposures, older rats showed behavioral deficits, losses of synapses—the junctions between nerve cells—and earlier and larger growth of amyloid plaques.

> **"We may not know all the details, and very much of the research is incomplete. But incomplete doesn't mean inconclusive."**
>
> **—Amedeo D'Angiulli**

Neurobiologist Caleb Finch, at the University of Southern California in Los Angeles, and behavioral neuroscientist Ben Nephew, at the Worcester Polytechnic Institute in MA, are producing similarly concerning results in the rodent brain. They're seeing reduced adult nerve stem cell production and inflammatory responses that speed up the production of amyloid plaques. Their animals also show decreased play behavior and social grooming and increased anxiety-related behaviors (15). Costa's team has found that mice exposed to diesel exhaust during prenatal and early postnatal life have lower levels of reelin, a protein important for brain development, as well as morphological changes in the layering of the cortex (16). "That is very similar to what you find in autism," he says.

Saving Minds and Money

Nicolai Kuminoff, an environmental economist at Arizona State University (ASU) in Tempe, had spent much of his career thinking about the benefits of reducing air pollution. Yet, again, impacts on the brain hadn't been a top priority until he saw the emerging animal and epidemiological studies. He and some ASU colleagues believed insights from economic studies could build on that work.

They recently leveraged a natural experiment to seek evidence of a causal relationship between air pollution and dementia in humans (17). In the mid-2000s, the EPA began to enforce a maximum PM2.5 threshold around the country. Local regulators in many areas were forced to improve air quality. In areas where pollution levels were just below the threshold, however, no cleanup was required.

Epidemiological studies can face a major limitation: People often end up living in more or less polluted areas as a result of factors such as education and income that might also influence health outcomes. The team sidestepped that issue by taking advantage of these resulting higher and lower exposure groups, connecting EPA air quality data to Medicare data for nearly 7 million Americans between 2004 and 2013. They wanted to know whether cutting air pollution could reduce rates of dementia.

After controlling for a range of health and socioeconomic factors, including hypertension, education, and housing values, they found that relatively fewer older people in counties with newly improved air quality developed dementia compared with counties without recent changes. Overall, evidence linked the federal regulation to nearly 182,000 fewer people with dementia in 2013. The team calculated that reduction to be worth an estimated $214 billion based on assumptions about the value of life and health. They further determined that additional regulation would avoid even more cases of dementia. In fact, dropping air pollution in areas with lower initial concentrations produced some of the largest risk reductions, notes Kuminoff.

The federal government has been incorporating a value for improving health into its cost–benefit calculations for avoided cases of asthma and heart disease but has not yet accounted for the link between air pollution and dementia. The EPA doesn't cite the impact of air pollution on the brain, nor do US regulations such as the 2015 Clean Power Plan. "We've almost entirely ignored the brain," says Finch. Shifting Alzheimer's disease onset earlier by a year or two, he adds, "could be an immense cost."

He and other researchers continue to explore many unanswered questions, such as which pollutants or hitchhiking metals are the most potent in damaging the brain and whether there are developmental windows of higher susceptibility. Gender may play a role, too: Cory-Slechta has found that exposures after birth cause far more change in the brains of male mice than females.

Kuminoff and his colleagues are now investigating how impacts of air pollution on the brain vary across regions of the country and demographic groups. The particulate matter contaminating East Coast air is predominantly generated by coal and natural gas, for example, whereas manufacturing and motor vehicle traffic contribute more particles to the air in the West Coast. "One possibility is that it's not the size of particulates but what's in it that matters most," Kuminoff says. His team is also asking questions such as whether someone could reverse the effects of their exposure if they move from a place with dirty air to a cleaner area—similar to quitting smoking—or whether air pollution may play a role in the persistence of socioeconomic status across generations. Damage to the brain at an early age, explains Kuminoff, may cause a downward spiral of poor education and income that pushes people to stay in polluted areas throughout their lives.

Everyone seems to agree that although the research remains at an early stage, enough evidence exists now to take action. "We may not know all the details, and very much of the research is incomplete. But incomplete doesn't mean inconclusive," says D'Angiulli.

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