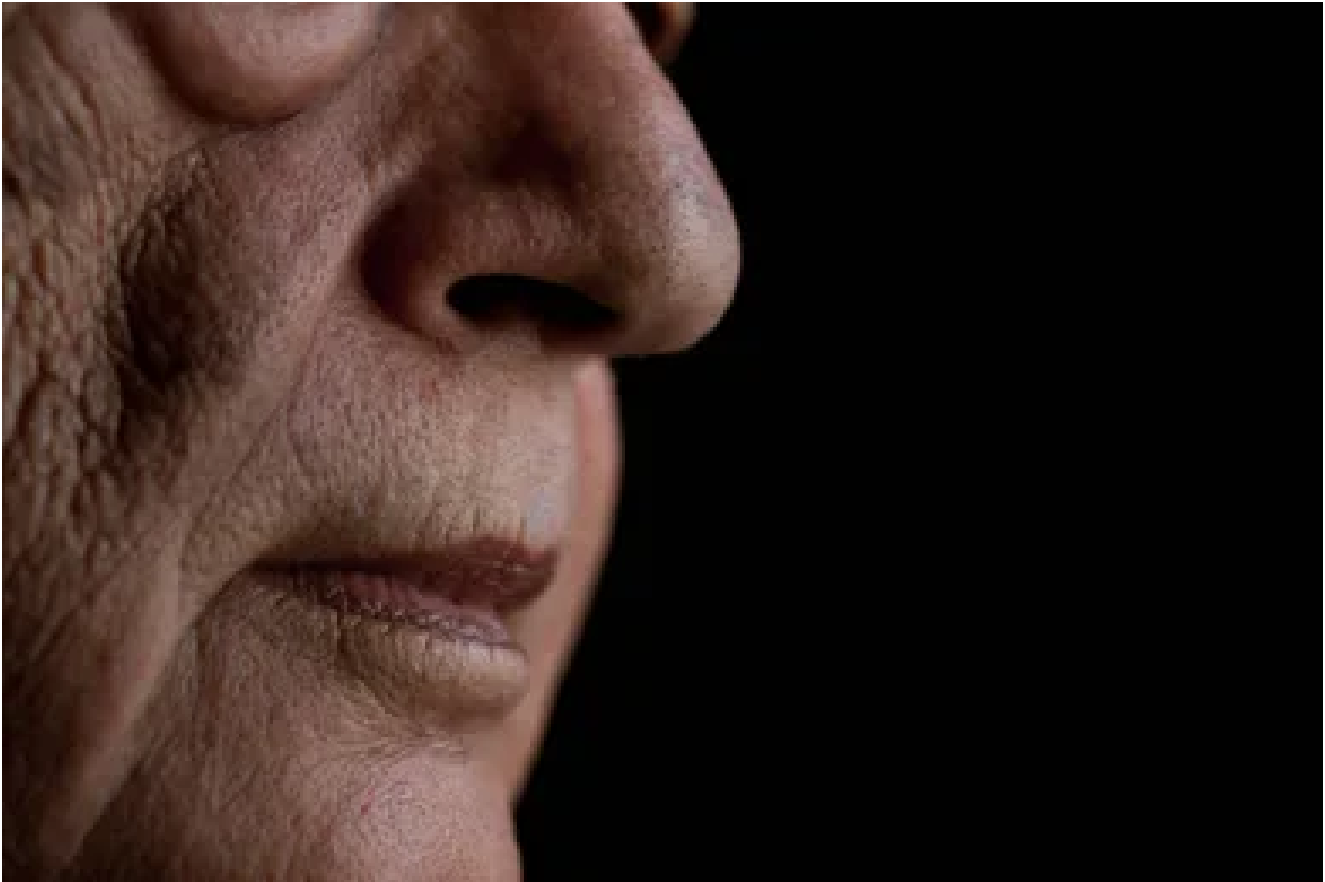


NEUROSCIENCE

Smell Test May Sniff Out Oncoming Parkinson's and Alzheimer's

How an unlikely clue could help solve the mystery of two devastating disorders

By David Noonan on June 12, 2017



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Sight and hearing get all the glory, but the often overlooked and underappreciated sense of smell—or problems with it—is a subject of rapidly growing interest among scientists and clinicians who battle Alzheimer's and Parkinson's diseases. Impaired smell is one of the earliest and most common symptoms of both, and researchers hope a better understanding will improve diagnoses and help unlock some of the secrets of these incurable conditions.

The latest offering from the burgeoning field is a review published in June in *Lancet Neurology*. It proposes neurotransmitter dysfunction as a possible cause of smell loss in a number of

neurodegenerative diseases, including Alzheimer's and Parkinson's.

More than 90 percent of Parkinson's patients report some level of olfactory dysfunction. And because problems with smell progress in Alzheimer's, nearly all of those diagnosed with moderate to severe forms of the illness have odor-identification issues. "It's important, not just because it's novel and interesting and simple but because the evidence is strong," says Davangere Devanand, a professor of psychiatry and neurology at Columbia University, who was not an author of the paper. His most recent paper on the subject, a review, was published in the *American Journal of Geriatric Psychiatry* in December.

Studies have shown impaired smell to be even stronger than memory problems as a predictor of cognitive decline in currently healthy adults. It is especially useful for forecasting the progression from mild cognitive impairment (MCI) to full-blown Alzheimer's. According to the Alzheimer's Association, approximately 15 to 20 percent of people older than 65 have MCI. About half of them go on to develop Alzheimer's, Devanand says—and the sooner they are identified, the earlier doctors can begin interventions, including treatment with the few existing Alzheimer's drugs.

Among Parkinson's patients, loss of smell occurs more often than the most common type of tremor. It can precede the classic motor signs of the disease by several years, and olfactory tests have been shown to do a better job than motor function tests when it comes to distinguishing Parkinson's patients from healthy control subjects. In fact, *not* having trouble with smell is often enough to rule out the disease. "If a person scores very well on a smell-identification test, then you can be pretty sure he or she is not going to have Parkinson's, at least within the next four years," says neurologist and researcher G. Webster Ross of the Veterans Affairs Pacific Islands Health Care System.

As eager as they are to raise awareness of the connection between olfactory dysfunction and neurodegenerative disease, experts in the field are also quick to point out that problems with smell are common in the general population and do not always indicate a higher risk of developing Parkinson's or Alzheimer's. The number-one cause of long-lasting or even permanent smell loss is the common head cold, says Richard Doty, primary founder and director of the Smell and Taste Center at the University of Pennsylvania and author of the review. Doty, a professor of otorhinolaryngology, invented the University of Pennsylvania Smell Identification Test (UPSIT), a 40-odor scratch-and-sniff test that has become the gold standard for diagnosing olfactory dysfunction. Additional causes include other types of viral infections, a history of

smoking, head injuries and getting older. Indeed, according to Doty, about half the U.S. population between the ages of 65 and 80 have some demonstrable loss of smell. If subjects are older than 80, that number goes up to about 75 percent.

Once colds and other common causes are ruled out, family doctors and general practitioners might order a smell test and start to consider the rarer and far more serious possibilities. “But it has to be done in the context of a complete medical history and a proper evaluation,” Devanand says. “You can’t just randomly give it.” For neurologists such as Devanand and Ross, the results of a smell test can initiate a workup or help confirm a diagnosis. “It’s really a subgroup of the population where this is useful for detecting or predicting future cognitive decline or Parkinson’s,” Doty says. Impaired smell is just one of several early, nonmotor signs that Ross looks for when he faces a potential Parkinson’s case. Others include chronic constipation (which he says may occur as much 12 years prior to diagnosis) as well as slow reaction time on a computer test and excessive daytime sleepiness.

Separate from its link to neurodegenerative disease, olfactory dysfunction has been associated with an increased risk of death, independent of other causes, including dementia, in four studies of older adults. Whereas the reasons for the effect remain unclear, a large study led by Devanand suggests “safety and nutritional issues associated with the loss of smell”—the inability to smell smoke, for example, and lack of interest in food from loss of taste—could be contributors. In a 2014 study at the University of Chicago, researchers wrote, “We believe olfaction is the canary in the coal mine of human health.”

The simplicity and low cost of a smell test—\$26.95 retail, before additional doctor or hospital charges—make it especially appealing in neurology, a field dominated by positron-emission tomography scans, dopamine transporter single-photon emission computed tomography imaging and other expensive technologies. Because it is so economical, Devanand says researchers should incorporate olfaction testing into studies that look at other Alzheimer’s risk factors in large populations. He has applied for a grant to do just that in an upcoming Columbia study involving 3,000 subjects. He would also like to see more studies that directly compare olfaction testing with costly and invasive procedures such as brain scans and spinal taps.

In addition to its importance as an early and reliable warning of Alzheimer's and Parkinson's, impaired smell offers a window into the underlying mechanisms of the two diseases. "If somebody has very mild Alzheimer's and dies," Devanand says, "on autopsy, we will see the pathology of Alzheimer's—the tangles and plaques—in the olfactory bulb." The presence of the dead, snarled nerve cells and sticky protein fragments characteristic of Alzheimer's in the main smell-processing structures of these deceased patients could suggest the disease gets its start in the olfactory system. There is some evidence for this, Devanand says, "but it's not overwhelming." Similarly, Doty says there is an argument to be made for calling the olfactory system the origin of Parkinson's but adds this is "probably an oversimplification."

Such caution and uncertainty are hardly surprising at this point, given the complexity of the anatomy involved. The olfactory system comprises six million to 10 million receptor cells (of which there are nearly 400 different types) and links to multiple brain structures and neural pathways, including those involved in memory, emotion and movement. Doty draws on more than 30 years of research to describe the role faulty brain chemistry, particularly that involving the neurotransmitter acetylcholine, might play in the smell impairment that accompanies neurodegenerative disease. For his part, Ross wonders if perhaps the nasal mucosa—the layer of mucus lining the inside of the nose—"may be a conduit through which some environmental toxin can gain access to the brain," potentially triggering Parkinson's and disrupting smell along the way.

There may not be answers yet, but more researchers are asking questions about the relation between smell and neurodegenerative diseases. "In the past," Devanand says, "most neurologists thought, 'Maybe there's something there statistically in a paper, but it's a bit flaky.'" Those days are gone, he says, thanks to consistent results from researchers in the U.S. and Europe—findings that confirm the importance of an unlikely clue in the fight against devastating disorders.