Experts probe possible reasons for loss of smell

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Studies have shown that loss of the sense of smell can be among the first warning signs of diseases such as Alzheimer's and Parkinson's. Now a researcher at the Perelman School of Medicine at the University of

Pennsylvania wants to shift the search for clues about this process back even further, to find out if there is a common factor responsible for the loss of smell that may also serve as an early warning signal for a number of neurodegenerative diseases. In a review published online in *Lancet Neurology*, Richard L. Doty, PhD, a professor of Otorhinolaryngology and director of the Smell and Taste Center, cites evidence that the common link could be damage to neurotransmitter and neuromodulator receptors in the forebrain - the front part of the brain.

"We need to retrace the steps of the development of these diseases," Doty said. "We know loss of smell is an early sign of their onset, so finding common factors associated with the smell loss could provide clues as to the pre-existing processes that initiate the first stages of a number of neurodegenerative diseases. An understanding of such processes could provide novel approaches to their treatment, including ways to slow down or stop their development before irreversible damage has occurred."

Currently, it's is generally believed that the smell loss of various neurodegenerative diseases is caused by disease-specific pathology. In other words, different diseases can bring about the same loss of smell for different reasons. Doty's review - the first of its kind - looked at many neurodegenerative diseases with varying degrees of smell loss and sought to find a common link that may explain such losses. He considered physiological factors as well as environmental factors like air pollution, viruses, and exposure to pesticides.

"Ultimately, as each possibility was evaluated, there were cases where these factors didn't show up, which ruled them out as potential universal biomarkers."

Doty did find compelling evidence for a neurological solution: Damage to the neurotransmitter and neuromodulator receptors in the forebrain -

most notably, a system employing the neurochemical acetylcholine. Neurotransmitters are the chemicals that send signals throughout the brain. Neuromodulators influence the activity of neurons in the brain. The receptors receive the signals, and if they are damaged, it hurts the brain's ability to process smells normally.

"The good news is we can assess damage to some of the systems by evaluating their function in living humans using radioactive neurochemicals and brain imaging processes such as positron emission tomography (PET)," Doty said. "Unfortunately, few data are currently available, and the historical data of damage to neurotransmitter/neuromodulator systems, including cell counts from autopsy studies, are limited to just a few diseases. Moreover, quantitative data on a patient's olfactory status is rarely available, especially prior to disease diagnosis."

Doty said the lack of early data is a problem across the board in the search for factors that may explain smell loss.

"Smell testing isn't part of a standard check-up, and people don't recognize a smell problem themselves until it's already severe," Doty said. "Research now starting in Japan will be testing thousands of people over the course of the next few years that will better define associations between changes in smell and a wide variety of physiological measures in older populations."

"If a universal factor does exist, the benefits for patients would be obvious," Doty said. "Damage to the neurotransmitter and neuromodulator receptors shows promise as one possibility, but we need more research in this area to truly answer the question. It could be the key to unlocking better understanding of neurological disease."

More information: Richard L Doty, Olfactory dysfunction in

neurodegenerative diseases: is there a common pathological substrate?, *The Lancet Neurology* (2017). DOI: 10.1016/S1474-4422(17)30123-0