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Brain regions related to smell show decline following mild COVID-19

Researchers from the University of Oxford have used data from UK Biobank participants to look at changes to the brain on average 4.5 months after mild SARS-CoV-2 infection.

The findings, published in *Nature*, reveal tissue damage and greater shrinkage in brain areas related to smell. This new insight into the damaging effects of COVID-19 will contribute to our overall understanding of how the disease spreads through the central nervous system. Whether these effects persist in the long term, or are partially reversed, requires further investigation.

Research has already shown that COVID-19 may cause brain-related abnormalities, but most studies have focused on hospitalized patients with severe disease, and have been limited to post-infection data. The effects of SARS-CoV-2 on the brain in milder (and more common) cases were unknown until now, and investigating these cases could reveal possible mechanisms that contribute to brain disease or damage.

Professor Gwenaëlle Douaud and colleagues investigated changes in the brains of 785 participants in UK Biobank, a large-scale biomedical database and research resource. Participants were aged 51–81 and underwent two brain scans, on average 38 months apart, as well as cognitive tests. A total of 401 participants tested positive for infection with SARS-CoV-2 between their two scans, of whom 15 were hospitalised. The remaining 384 individuals, who did not get infected, were similar to the infected group in age, sex, and many risk factors, including blood pressure, obesity, smoking, socio-economic status and diabetes.

The study, led by the Wellcome Centre for Integrative Neuroimaging at the University of Oxford, identified a number of effects, on average 4.5 months following infection, including a greater reduction in grey matter thickness in the regions of the brain associated with smell (the orbitofrontal cortex and parahippocampal gyrus). UK Biobank participants who had COVID-19 also displayed evidence of greater tissue damage in regions connected with the primary olfactory cortex, an area linked to smell, and a reduction in whole brain size. These effects ranged from 0.2 to 2% additional change compared with the participants who had not been infected.

On average, the participants who were infected with SARS-CoV-2 also showed greater cognitive decline between their two scans, associated with the atrophy of a specific part of the cerebellum (a brain structure) linked to cognition. Separately, the authors studied people who developed pneumonia not related to COVID-19, showing that the changes were specific to COVID-19, and not due to the generic effects of contracting a respiratory illness.

Prof. Gwenaëlle Douaud, lead author on the study, said: ‘Using the UK Biobank resource, we were in a unique position to look at changes that took place in the brain following mild—as opposed to more moderate or severe—SARS-CoV-2 infection. Despite the infection being mild for 96% of our participants, we saw a greater loss of grey matter volume, and greater tissue damage in the infected participants, on average 4.5 months after infection. They also showed greater decline in their mental abilities to perform complex tasks, and this mental worsening was partly related to these brain abnormalities. All these negative effects were more marked at older ages. A key question for future brain imaging studies is to see if this brain tissue damage resolves over the longer term.’

Prof. Stephen Smith, senior author on the study, also from the Wellcome Centre for Integrative Neuroimaging, commented: 'Another strength of this study is that it investigated the same people at two different times. Importantly here, the first scan of UK Biobank participants was obtained before they became infected with SARS-CoV-2, and the second scan after infection. The fact that we have the pre-infection scan helps us distinguish brain changes related to the infection from differences that may have pre-existed in their brains.'

Prof. Naomi Allen, Chief Scientist at UK Biobank, said: 'The UK Biobank COVID-19 Repeat Imaging study is the only study in the world to be able to demonstrate "before vs after" changes in the brain associated with SARS-CoV-2 infection. Collecting a second set of multi-organ imaging scans from some people who had been infected with SARS-CoV-2 and from others who had not been infected has generated a unique resource to enable scientists to understand how the virus affects internal organs. We are incredibly grateful to all of the UK Biobank participants for taking the time to be imaged more than once, to enable researchers to gain valuable insights into long term health effects of SARS-CoV-2 infection. '

These findings may be the hallmarks of the degenerative spread of COVID-19, either via pathways related to the sense of smell, inflammation or immune response of the nervous system, or a lack of sensory input owing to a loss of smell. The future vulnerability of the brain regions affected in these participants requires further investigation.

ENDS

Notes to Editors:

For further information or to arrange an interview, please contact the **University of Oxford press office** at news.office@admin.ox.ac.uk or on +44 (0)1865 280528.

The paper 'SARS-CoV-2 is associated with changes in brain structure in UK Biobank' by Douaud *et al*. will be published in *Nature* on March 7. Link to the paper: https://www.nature.com/articles/s41586-022-04569-5 (doi:10.1038/s41586-022-04569-5).

Image caption: The red-yellow regions are the parts of the brain that shrink the most in the 401 SARS-CoV-2 infected participants, compared with the 384 non-infected participants. These areas are related to the sense of smell, and include the parahippocampal gyrus, the orbitofrontal cortex and the insula. We present the results in half of the brain (the left hemisphere, with inferior, side and medial views), on an average brain that has been "inflated" to show the nooks and crannies of the brain. *Credit: G. Douaud, in collaboration with Anderson Winkler and Saad Jbabdi, University of Oxford and NIH.*

This study was primarily funded by a Wellcome Trust Collaborative Award, "Integrative imaging of brain structure and function in populations and individuals".

The study was led by **Prof. Gwenaëlle Douaud**, from the Wellcome Centre for Integrative Neuroimaging (WIN), an Associate Professor at the Nuffield Department of Clinical Neurosciences (NDCN) and Research Fellow at Green Templeton College, and **Prof. Stephen Smith**, also from the Wellcome Centre for Integrative Neuroimaging, and Professor of Biomedical Engineering at the Nuffield Department of Clinical Neurosciences, both at the University of Oxford.

The **Wellcome Centre for Integrative Neuroimaging** (WIN), established in 2017, is a multi-disciplinary neuroimaging research facility. WIN aims to bridge the gap between laboratory neuroscience and human health, by performing multi-scale studies spanning from animal models through to human populations. The Analysis group within the WIN is dedicated to new methodologies for the analysis of

functional and structural brain imaging data and is leading the neuroimaging in the UK Biobank project: determining the imaging hardware setup, imaging protocols and post-processing pipeline, in consultation with the wider imaging community.

The **Nuffield Department of Clinical Neurosciences** has an established research and teaching portfolio with a national and international reputation for excellence. It comprises five sections: the Centre for the Prevention of Stroke & Dementia, the Division of Clinical Neurology, the Nuffield Division of Anaesthetics, the Nuffield Laboratory of Ophthalmology and the Wellcome Centre for Integrative Neuroimaging. The Department is based in the John Radcliffe Hospital and has developed a highly integrated and interdisciplinary environment in which research, teaching, clinical training and clinical care interact. This enables new approaches to the understanding, diagnosis and treatment of brain diseases.

UK Biobank is a large-scale biomedical database and research resource containing genetic, lifestyle and health information from half a million UK participants. UK Biobank's database, which includes blood samples, heart and brain scans and genetic data of the 500,000 volunteer participants, is globally accessible to approved researchers who are undertaking health-related research that's in the public interest.

UK Biobank recruited 500,000 people aged between 40-69 years in 2006-2010 from across the UK. With their consent, they provided detailed information about their lifestyle, physical measures and had blood, urine and saliva samples collected and stored for future analysis.

UK Biobank's research resource is a major contributor in the advancement of modern medicine and treatment, enabling better understanding of the prevention, diagnosis and treatment of a wide range of serious and life-threatening illnesses – including cancer, heart diseases and stroke. Since the UK Biobank resource was opened for research use in April 2012, over 22,500 researchers from +90 countries have been approved to use it and more than 2,000 peer-reviewed papers that used the resource have now been published.

UK Biobank is generously supported by its founding funders the Wellcome Trust and UK Medical Research Council, as well as the British Heart Foundation, Cancer Research UK, Department of Health, Northwest Regional Development Agency and Scottish Government. The organisation has over 150 dedicated members of staff, based in multiple locations across the UK.

Find out more here: http://www.ukbiobank.ac.uk

University of Oxford

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Oxford is world-famous for research and teaching excellence and home to some of the most talented people from across the globe. Our work helps the lives of millions, solving real-world problems

through a huge network of partnerships and collaborations. The breadth and interdisciplinary nature of our research alongside our personalised approach to teaching sparks imaginative and inventive insights and solutions.

Through its research commercialisation arm, Oxford University Innovation, Oxford is the highest university patent filer in the UK and is ranked first in the UK for university spinouts, having created more than 200 new companies since 1988. Over a third of these companies have been created in the past three years. The university is a catalyst for prosperity in Oxfordshire and the United Kingdom, contributing £15.7 billion to the UK economy in 2018/19, and supports more than 28,000 full time jobs.