- **Who are the participants of this study?**

The 785 UK participants had already been scanned for UK Biobank before the start of the pandemic, and were invited back for a second scan as part of the COVID-19 re-imaging study. They were **aged between 51 and 81 years old**. Lateral flow tests and/or medical records showed that **401 of them had become infected with SARS-CoV-2 *between* their two scans**. They became infected on average 4.5 months before their second scan. Only 15 (4%) of these 401 infected participants were hospitalised.

The "control" group, who did not become infected between their two scans, were similar in age, sex, and many risk factors, including blood pressure, obesity, smoking, socio-economic status and diabetes, to the infected group.

- **What are the main results of this study?**

Our study was "longitudinal", i.e., it looked at the same people at two different timepoints separated on average by 3 years. We found that the brains of the participants who had been infected showed **changes between their two scans that were different** from changes seen in the non-infected participants. Infected participants showed **greater loss of grey matter, as well as greater abnormalities in the brain tissue**.

These differences were mainly found in specific regions of the brain, the olfactory areas, which are **related to the sense of smell**. We also identified some global changes, such as in the overall size of the brain, which shrunk more in the infected participants than in the non-infected participants. All of these effects were **greater for older infected participants**.

- **How big are the changes associated with SARS-CoV-2 infection?**

It depends on the different regions of the brain, but, on average, the infected participants showed an ***additional* 0.2% to 2% loss or tissue damage** compared with the non-infected participants. For example, infected participants may have lost 2.9% grey matter in a given brain region, whereas non-infected participants will have lost only 0.9% over the same 3 year-period. To make sense of how big or small these effects are, it is worth putting them in the context of what happens in healthy ageing: it has been shown previously that people lose each year about 0.2% to 0.3% of grey matter in regions related to memory[1].

- **What makes it different from other brain imaging studies?**

This study is different for two main reasons:

- The first is that it is "longitudinal", i.e., **a study that investigates the same people at different times**. Importantly here, the first scan in our participants was obtained

before they became infected with SARS-CoV-2, and the second scan *after* they had been infected. This means that the changes observed in their brain are associated with the infection. The fact that we have the scan pre-infection also helps us distinguish brain changes related to the infection from differences that may have pre-existed in their brain.

- The second is that the bulk of (brain) imaging studies have focused on moderate to severe cases of infection, scanning people hospitalised with COVID-19. On the contrary, **the vast majority of the infected participants in our study (96%) had not been hospitalised**, and might not even have had symptoms, so could be considered as having had **a mild infection**.

- **Was there any difference in mental abilities?**

Yes. We found that the infected participants showed a **greater decline in their ability to perform complex tasks** compared with the non-infected participants. This difference between infected and non-infected participants was even **more marked at older ages**.

- **What can cause these abnormalities in the brain?**

The cause of these abnormalities might be **loss of smell** in the infected participants. Indeed, repeated olfactory loss has been shown in previous to studies to lead to loss of grey matter in brain regions related to olfaction[2,3]. Unfortunately, we do not have information about the symptoms of the infected participants, such as loss of smell.

Another explanation could be **the effect of the virus itself**, either because it invades the brain, or because it causes inflammation or immune reactions[4,5]. It is still unclear why such invasion or inflammatory/immune reactions should be mainly seen in specific regions of the brain, but not others.

- **Is this "brain damage" reversible?**

Since the abnormal changes we see in the brain of the infected participants might be related to their loss of smell, it is possible that recovering their smell might lead to these brain abnormalities becoming less marked over time. Similarly, it is likely that the harmful effects of the virus (whether direct, or indirect via inflammation or immune reaction) decrease over time after infection. There is some indication, from small previous studies, that issues seen in functional brain imaging may improve in part more than 6 months after infection[6,7].

- **Are these findings related to "long COVID"?**

The definition of "long COVID" is not entirely clear at the moment, but it is based on a range of symptoms for which we do not have any information unfortunately. Our participants were scanned again, on average, four and a half months after becoming infected, so it is possible that some of them were experiencing "long COVID", but we cannot say how many did, or know which ones.

- **What is the effect of the vaccines?**

We did not have access to this specific clinical information. Even if we knew the date of the vaccines received by our participants, a large majority in our study became infected *before* vaccines were made available in the UK, so their protective effects would be hard to assess.

- **Have the effects of different variants been explored?**

We had no formal way of assessing the strain responsible for the infection, so we did not explore this question. Our study probably mainly captured the effects associated with the original strain and with the Alpha variant, considering the period of SARS-CoV-2 infection covered (March 2020 – April 2021). A small minority of the participants were likely to have been infected with the original strain, and a majority with the variants of concern present in the UK from October 2020 onwards (predominantly Alpha, but also Beta and Gamma). Presumably very few participants, if any, were infected with the Delta variant, which only appeared in the UK in April 2021.

- **Could the same be seen in kids?**

We have only explored the effects associated with mild SARS-CoV-2 infection in older adults, as our participants were aged between 51 to 81 years old at the time of their second brain scan (which took place on average 4 months or so after infection). We do not know whether the same damaging impact would be seen in kids.

- **Could the same be seen with other viruses, e.g., influenza?**

In our study, we have focused on the changes in the brain associated with mild SARS-CoV-2 infection. To our knowledge, no other brain imaging study has looked at comparing scans *before* and *after* infection from any other viruses, so it is not possible to say at the moment whether similar changes could occur with, e.g., influenza.

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