

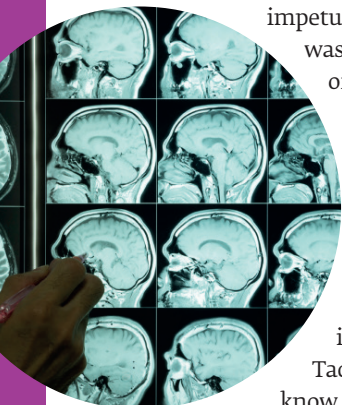
While the effects and after-effects of COVID-19 infection have been studied non-stop since the pandemic was declared a year ago, two areas that perhaps haven't received so much scrutiny have been the neurological and psychiatric reverberations.

That changed recently with the publication on *medRxiv* of the paper *Six-month Neurological and Psychiatric Outcomes in 236,379 Survivors of COVID-19* (not yet peer-reviewed). Looking at the incidence rates and relative risks of neurological and psychiatric sequelae among the cohort, it estimated that incidence at six months among patients was 33.6%, with 12.8% receiving their first such diagnosis. The conditions included intracranial haemorrhage, stroke, Parkinson's, encephalitis, dementia, anxiety, psychotic disorders, substance misuse and insomnia.

Data were obtained from the TriNetX electronic health records network from across the US. Some 80% of the patients (190,077) were not hospitalised by the infection; the remaining 46,302 were.

The trigger

The research team, drawn from the University of Oxford and the city's NHS hospitals, was headed by Dr Maxime Taquet in the department of psychiatry at the University of Oxford. The impetus for the research was the known risk of secondary neurological and psychiatric conditions. "Any infection, severe or otherwise, can be a trigger for psychiatric illness," says Taquet. "We also know that a severe



NEUROLOGICAL REVERBERATIONS

Dr Maxime Taquet discusses his research into COVID-19 and secondary neurological and psychiatric conditions.

infection can cause patients to have conditions such as delirium, which is a transient change in the mental state. That's mostly in the elderly – they might be very confused, for instance. That in itself can be a risk factor. So in that broad sense, any health event, including infection, can be a trigger for psychiatric and neurological diseases."

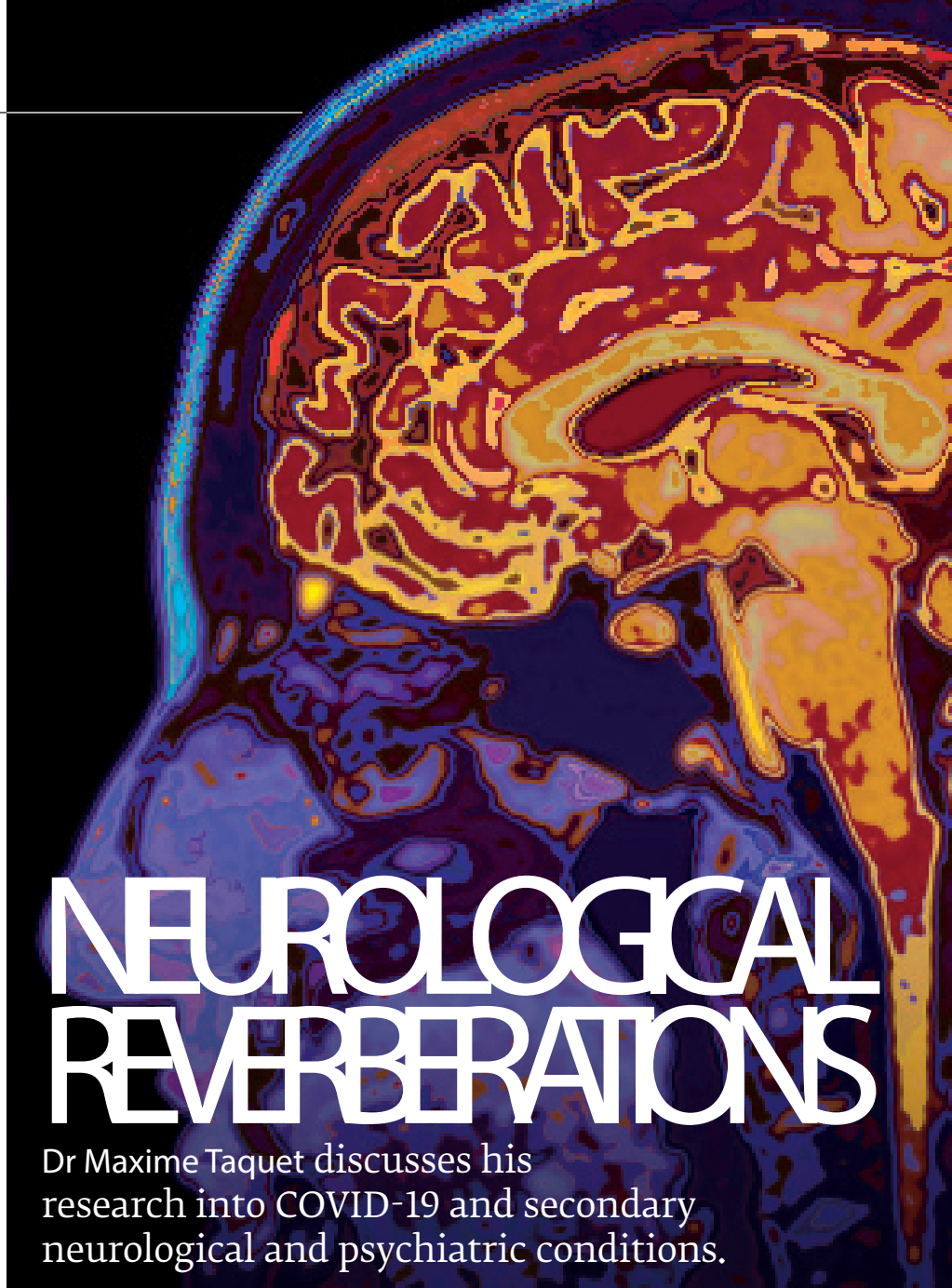
There are also historical markers. Research found that in the six years following the Spanish flu pandemic of 1918-19 the number of patients hospitalised in Norway for the first time with mental disorders rose significantly. In the US, suicide rates were heavily related to Spanish flu up to 1920. Here in the UK, flu survivors were reported

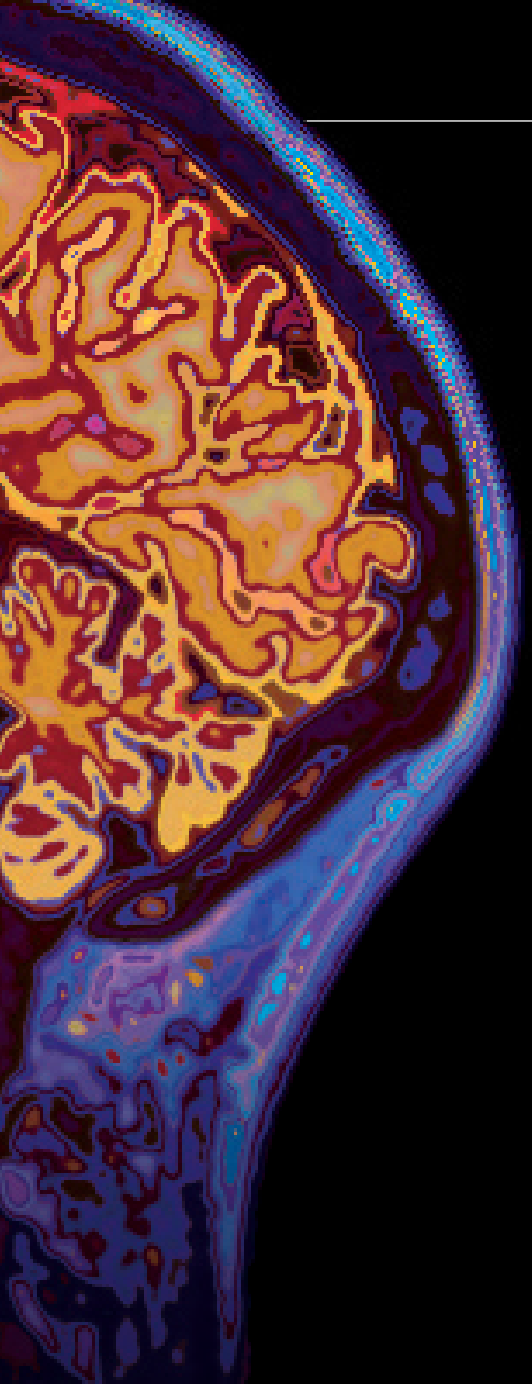
to suffer depression, neuropathy, neurasthenia, meningitis, never cell degeneration, and impaired vision.

"That was one of the questions that we had," says Taquet. "Is COVID-19 one of those events that has a specific association with neurological and psychiatric conditions? The answer seemed to be yes, so the real purpose of the study was to look at the extent of the issue and to quantify it."

Establishing a link

A handful of earlier studies helped to establish the link between COVID-19 infection and neurological and psychiatric conditions, not least from Taquet and his colleagues themselves. "We had a previous





study published in *The Lancet Psychiatry* where we looked at the three-month outcomes of patients with COVID-19 in terms of psychiatric illnesses only. We were quite surprised by the extent to which it was associated with these illnesses. But that finding has now been replicated in different studies in different settings.”

This latest study has taken a step further by including neurological conditions and by looking at a much larger population over a longer period. “We looked at six months of follow-up rather than three months after diagnosis. It was quite surprising to see that the diagnosis of neurological and psychiatric conditions carried on increasing. We thought that it might reach a plateau.”

The paper reports: “like the neurological outcomes, the psychiatric sequelae of COVID-19 appear widespread, and persist to and probably beyond six months.”

Risk of stroke

Perhaps even more surprising is the extent to which COVID-19 infection is associated with certain neurological diseases. “We looked at the incidence of stroke, and what we found is that among all patients with COVID-19, not just the most severely affected and not even just those who are hospitalised, one in 50 develop a stroke. That’s quite a big number. The association with stroke has been mentioned in the literature before, but this is probably the first time that we have put an actual number to that. Again, rather than just the presence of those sequelae, I think the surprising thing is the extent to which that’s the case.”

Why might an infection such as COVID-19 raise the risk of stroke? “What’s been found and highlighted in the literature about COVID-19 is that it tends to disturb the coagulation system in people’s bodies. A blood clot can be a good thing if you are bleeding, but it can also be a bad thing if it’s overdriven. That might cause issues such as a pulmonary embolism. We know that quite a few patients who died of COVID-19 actually died of a pulmonary embolism, so if those clots can form in the lungs they can also form in the heart or the brain and then cause a stroke.”

Conclusion

The implications of the teams’ research are that a substantial number of post-COVID-19 patients are going to require care in the months after their recovery and possibly much longer. “It’s going to be important to follow up those patients to see what the long-term outcomes are. For example, anxiety, depression and psychiatric disorders come in all shapes and sizes, as do many of the neurological diseases.

DR MAXIME TAQUET



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- ✓ Research fellow, Harvard Medical School
- ✓ Master’s degree in engineering, Simon Fraser University (Canada)
- ✓ Bachelor’s degree in engineering, UCLouvain (Belgium).

So this is a key question: is it a short-lived episode, which is concerning in itself, or does it have a more prolonged course? That’s going to be important to establish and assess if we are to give patients the best available treatment.”

The limitations of the study data pose further questions. “We are only capturing those people who have presented to a healthcare facility and received a diagnosis by a clinician. We suspect that for psychiatric conditions, quite a lot of patients did not receive a diagnosis simply because they didn’t seek medical attention. That’s a reason for active

follow-up of COVID-19 patients, perhaps even screening them for signs of neurological and psychiatric conditions.”

Besides these issues, Taquet says he and his colleagues want to look at aspects of long COVID-19 and more. “We’re also interested in surprising research showing that some antidepressants are effective at reducing the severity of COVID-19. That is puzzling and might point to shared mechanisms. Those are exciting and open research questions that I think we will be trying to tackle in future.”

