

## Introduction

The Florey welcomes the opportunity to make a submission to the Parliamentary Inquiry into Long COVID and Repeated COVID Infections.

The Florey is the largest brain research centre in the southern hemisphere; we have teams of researchers dedicated to building knowledge on a range of neurological and psychiatric conditions. Our expertise, collaborations and world-class facilities mean that our knowledge can be accelerated into impact – from finding treatments to changing clinical practice, improving the lives of people affected by brain conditions and mental health issues.

We are pleased to centre our submission around point four of the Inquiry's Terms of Reference:

- Research into the potential and known effects, causes, risk factors, prevalence, management, and treatment of long COVID and/or repeated COVID infections in Australia.

## Our expertise

A key area of expertise at The Florey is neurodegeneration – where cells in the brain break down, causing problems in how people behave, think, feel or move. Alzheimer's disease and Parkinson's disease are both examples of neurodegenerative conditions. How these conditions relate to long COVID is the key focus of our submission.

Professor Kevin Barnham is a leader at The Florey in the area of neurodegeneration and has expertise in developing neurotherapeutics for Alzheimer's (AD) and Parkinson's (PD). With over 200 scientific papers published, Professor Barnham's work has deepened our understanding of how these conditions function and how we can identify and develop potential treatments.

Neurodegenerative diseases are among the most expensive burdens to the Australian health system and have significant social costs. Any increase in the incidence of these diseases will have a devastating impact on an unprepared system.

A team of neuroscientists and clinicians, led by Professor Barnham at The Florey (and in partnership with the Royal Melbourne Hospital and Peter Doherty Institute) have been examining the potential link between COVID-19 and increased risk of PD disease.

## Our research

In August 2020, [a paper published by Professor Barnham and his team](#) said, ‘there are an ever-increasing number of reports of neurological symptoms in patients, from severe (encephalitis), to mild (hyposmia), suggesting the potential for neurotropism of COVID-19.’

At the time Professor Barnham said: “Although scientists are still learning how the SARS-CoV-2 virus is able to invade the brain and central nervous system, the fact that it’s getting in there is clear. Our best understanding is that the virus can cause insult to brain cells, with potential for neurodegeneration to follow on from there.”

The paper highlighted the potential long-term neurological consequences of COVID-19, and called for urgent action to be taken to have more accurate diagnostic tools available to identify neurodegeneration early on and a long-term monitoring approach for people who have been infected with the SARS-CoV-2 virus.

A lead researcher on Professor Barnham’s team, Dr Leah Beauchamp said: “We found that loss of smell or reduced smell was on average reported in three out of four people infected with the SARS-CoV-2 virus. While on the surface this symptom can appear as little cause for concern, it actually tells us a lot about what’s happening inside the brain and that is that there’s acute inflammation in the olfactory system responsible for smell.”

Inflammation is understood to play a major role in the pathogenesis of neurodegenerative disease and has been particularly well studied in PD. Further research into these illnesses may prove critical for future impacts of SARS-CoV-2.

“We believe that loss of smell presents a new way forward in detecting someone’s risk of developing PD early. Armed with the knowledge that loss of smell presents in around 90% of people in the early stages of PD disease and a decade ahead of motor symptoms, we feel we are on the right track,” added Dr Beauchamp.

Fast-forward to today, the questions the research team have about the effect of COVID-19 on the brain have advanced. It is now evident that there are serious long-term consequences of infection in multiple organ systems, such as post-acute COVID-19 syndrome, or ‘long COVID’.

There is particular concern around the neurological symptoms including loss of smell and memory complaints. Approximately 80% of those infected with SARS-CoV-2 virus report neurological dysfunction and 30% have persistent symptoms<sup>1</sup>. The long-term implications of these neurological symptoms require careful consideration as many of

them are known to be associated with increased risk of neurodegeneration or recognised as part of the prodrome of these disorders.

Mounting evidence that COVID-19 results in long-term neurological problems, a condition that has come to be known as post-COVID neurological syndrome (PCNS)<sup>1</sup>, is highly concerning for the capacity of Australian healthcare and social systems.

### **What we know from other research**

In a UK study of over 200,000 survivors of COVID-19, around 30% of subjects suffered from ongoing neurological problems<sup>2</sup>. The study identified 14 neurological and psychiatric adverse outcomes six months after the original infection, including intracranial haemorrhage\*; ischaemic stroke\*; parkinsonism\*; Guillain-Barré syndrome; nerve disorders; myopathies; encephalitis\*; dementia\*; psychosis, mood\*, and anxiety disorders\* (grouped and separately); substance use disorder; and insomnia\*. Many of these, denoted by the asterisks, are known to be in the prodrome of, or to increase the risk for, PD and AD diseases – the two most common neurodegenerative diseases in the world.

Emerging data are consistent with the hypothesis that COVID-19 will increase the risk of developing neurodegenerative diseases. Biomarkers associated with neurodegeneration such as phosphorylated tau protein and neurofilament light are elevated in the serum of patients with COVID-19 to similar levels observed in people with AD<sup>3</sup>. Post-mortem investigations of brain tissue from infected subjects found that the tissue exhibited an increase in 'Alzheimer's-like signalling'<sup>4</sup>. Neuronal vacuolization, a consequence of impaired autophagy and a classical feature of AD, has also been observed in the neuronal tissue of subjects that had COVID-19<sup>5</sup>. A recent post-mortem study showed that in ten out of ten brains examined, aggregated deposits of the amyloid- $\beta$  peptide (A $\beta$ ) was observed<sup>6</sup>. Aggregation of A $\beta$  has long been proposed as a cause of AD. An ageing brain is the major risk factor for AD and PD and a recent study undertaking whole transcriptomic analysis of human frontal cortex (an area of the brain associated with cognition) from COVID-19 subjects identified molecular signatures that are associated with an ageing brain<sup>7</sup>.

A recent study from the US Veterans Affairs, published in Nature Medicine<sup>8</sup>, has shown on follow up of over 150,000 people who had COVID-19 the risk of the subjects having a stroke, or developing AD or PD is substantially increased. This shows that the initial predictions from Florey researchers in August 2020 were correct.

These include downregulation of genes involved in synaptic function and cognition and upregulation of genes involved in immune processes (i.e. inflammation). These rapidly accumulating data raise the critical question: does COVID-19 accelerate brain ageing? It is worth noting that following the Spanish Flu pandemic of 1918/9 there

were still patients dealing with the neurological consequences of this disease in the 1960s - 40 years after the original pandemic ended<sup>9,10</sup>.

### **Big questions remain unanswered**

The implications of COVID-19 accelerating brain ageing are quite profound. In addition to the social costs of diseases such as AD and PD, they constitute an enormous economic burden - a current cost to the Australian economy exceeding \$25 billion per year. AD and PD are currently among the most expensive burdens to the Australian health system and any COVID-driven increase in the incidence of these degenerative brain diseases will add enormous additional pressure to an already stressed system.

With the onset of the more transmissible Omicron variant, the number of people diagnosed with COVID-19 is rising rapidly, but we are uncertain of the neurological fate of this ever-growing cohort. To efficiently plan for their health needs requires an understanding of the longer-term neurological consequences arising from this pandemic. Rapidly acquiring this knowledge would be greatly aided by the development of inexpensive diagnostic tools that are:

1. Capable of screening large numbers of patients
2. Able to identify people who are at risk of long-term neurological problems.

Our questions about how COVID-19 and long COVID affects the brain include:

- Are the neurological effects due to the virus's ability to live in brain tissue or are they due to the secondary effects of the virus?
- Does the virus 'unmask' neurodegenerative pathways or induce *de novo* disease?
- How do genetic and other risk factors impact on the risk that COVID-19 causes?
- What impact does repeated infection have on risk?
- What, if any, protection do current vaccines provide against neurological consequences?
- What other intervention strategies might be of benefit?

### **Concluding remarks**

An increase in incidence of PD and AD will put serious stress on the Australian health system, and although we are not sure on the size of the risk that long COVID poses to increasing neurodegenerative conditions, it is a risk nonetheless - and one that is concerning.

There is an urgent need to grow our understanding and answer the aforementioned questions and to do this we need a collaborative and multidisciplinary approach. This should make the most of the considerable resources and skills at several research centres, universities and hospitals across Australia.

**The Florey would welcome the opportunity to explain any of the research discussed in this submission further with members of the Standing Committee on Health, Aged Care and Sport, and would be happy to attend the next public hearing on the impacts of long COVID and repeated COVID-19 infections.**

## References

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