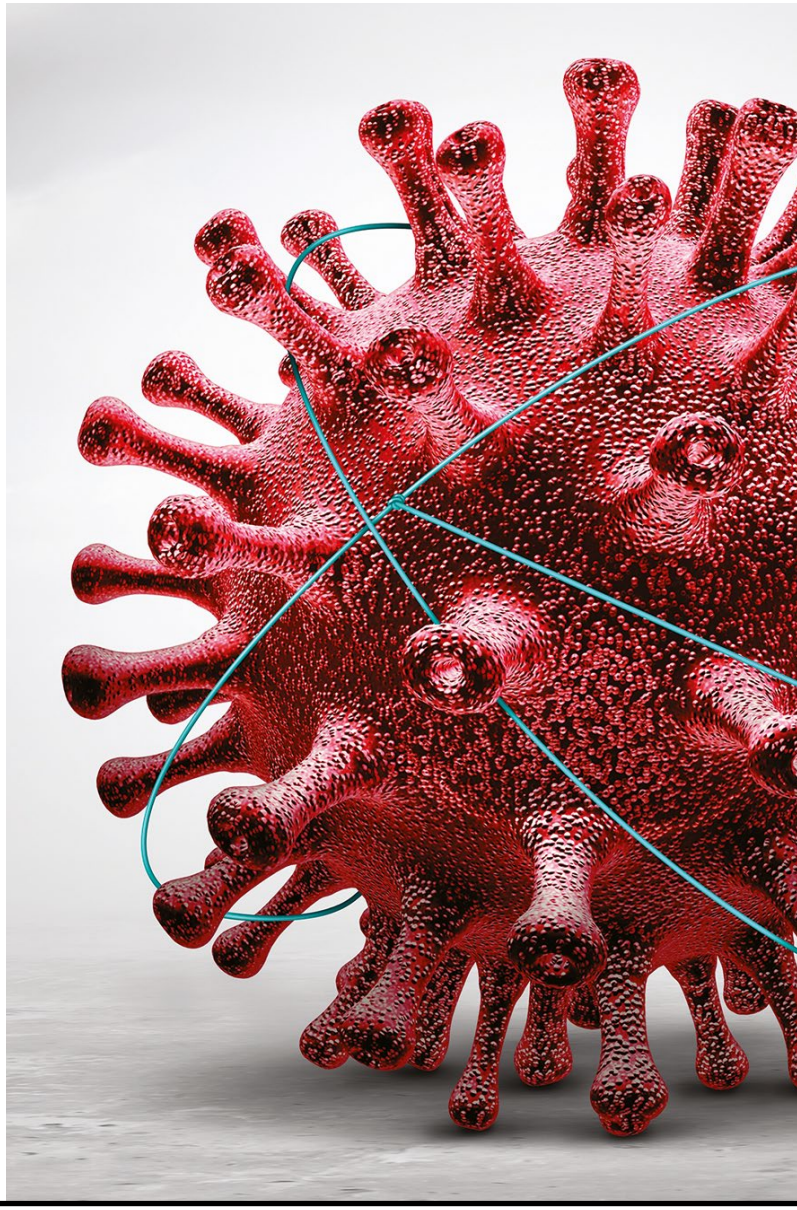
Post-COVID-19 cognitive impairment: a new target for drug development?

Dr. Paula Moran, **Dr, Kiri Granger**, **Dr J. Mark Treherne**, and **Dr. Jenny Barnett** explore the effects of long Covid-19 symptoms and what the opportunities are for drug developers working to treat post-Covid-19 cognitive impairment.



We are amidst a shift of focus from dealing with the acute impacts of the Covid-19 pandemic to tackling the 'long Covid-19' symptoms that may now represent greater future challenges for healthcare systems and patient quality of life. One particularly troubling consequence of Covid-19 is neurological change, which is commonly seen on brain scans even among people who experienced relatively mild illness. While much of the increase in psychiatric symptoms reported during the first months post-Covid-19 are tending to subside with time, long-term cognitive impairments do seem to persist for months and sometimes years in around 20-30% of people.

Moreover, in those suffering from long Covid-19, 'brain fog' is one of the most common and problematic symptoms, reported in around 70% of sufferers. With >80% of those affected saying brain fog is affecting their ability to return to work or education, this is also a substantial societal and economic issue.

Since post-Covid-19 /post-viral cognitive impairment is common and has a large impact on patient quality of life and ability to return to employment, is it now a plausible target for drug development efforts? To date, it seems that the likely mechanism of post-Covid-19 cognitive impairment is neuroinflammation triggered by the peripheral

/ systemic inflammation caused by the virus. Treating neuroinflammation is itself a major and attractive approach for current drug development given its role in several psychiatric and neurological conditions, and drugs designed to reduce neuroinflammation are already in development for numerous brain disorders. There is a clear opportunity to repurpose some of these candidates for preventative/prophylactic treatment for post-Covid-19 cognitive impairment. However, to invest in drug development for this condition, some significant methodological issues will need to be addressed.

The cognitive consequences of Covid-19

It's estimated that >90% of people in the UK have had a Covid-19 infection[1]. While somewhere around 100 people continue to die of (or with) Covid-19 each day[2], it's inevitable that much attention has now shifted to the wide-ranging and long-lasting symptoms known as 'long Covid' or PACS (post-acute sequelae of Covid-19)[3]. Long Covid-19 is commonly considered as persistence of symptoms beyond 12 weeks, and though the upper duration of timeframe is not yet known it is persisting beyond two years in at least some patients. Symptoms affect the brain, heart, lungs, GI tract and pancreas, are seen equally in vaccinated populations, and sometimes newly emerge after the acute infection has resolved. Given the numbers involved, these persistent symptoms likely represent great future challenges for healthcare systems.

A notable neuropsychiatric symptom that has emerged from patient reports is cognitive impairment, colloquially known as 'brain fog'. Estimates of the rate of cognitive impairment in Covid-19 patients vary widely but recent estimates suggest it affects 20-30% of all Covid-19 patients[4] and approximately 70% of those with long-Covid[5,6]. Memory, language, planning and attentional differences have been found between those that have and have not experienced Covid-19 infection and tend to be related to the severity of ongoing illness. These measured differences suggest that the cognitive consequences of Covid-19 are objectively measurable and not merely subjective experiences which could potentially be driven by other symptoms such as fatigue and low mood.

Increases in psychiatric symptoms such as mood and anxiety were indeed extremely common during the Covid lockdowns. The latest data suggest that these are now largely resolving, whereas cognitive impairment, psychosis, and dementia do not appear to be returning to pre-pandemic levels. A study[7] examined the electronic medical records of more than 1 million people from around the globe, looking at ongoing symptoms in those who had Covid-19 vs other respiratory illnesses. While common psychiatric disorders such as depression and anxiety were higher in those who recently had Covid-19, these differences disappeared over time. The most significant increased risk among adults aged 18 to 64 was for brain fog (6.4 % of people who had Covid-19 during the previous two years, vs. 5.5% of controls). Risk for brain fog remains higher in adults but not children at two years post-illness – the longest timeframe available. Notably, among over-65s who had had Covid-19, 4.5% developed dementia over the subsequent two years (vs 3.3% of those with other respiratory illnesses).

Cognitive impairment

Post-Covid cognitive impairment is associated with absenteeism from work and poorer quality of life[8]. Even mild cognitive impairment can have significant societal and economic consequences. In working age adults, up to 86% report that cognitive dysfunction and/or memory impairment was impacting their ability to work post-Covid[6]. The magnitude of impairment has been shown in some studies to be equivalent to clinically defined mild cognitive impairment (a condition that increases risk for dementia, showing greater impairment than expected for age but not as severe as dementia). The cost of accelerated or increased progression towards dementia is potentially enormous given that 1% of GDP is already spent on it.[9]

> **Given its prevalence and potential economic, societal and patient burden, post-Covid cognitive impairment seems an important target for treatment**

Biological mechanisms

Given its prevalence and potential economic, societal and patient burden, post-Covid cognitive impairment seems an important target for treatment, be that

through existing rehabilitations services, or digital, drug or biologic therapies. New therapeutics of course depend on an understanding of biological mechanisms. Luckily, some clear findings are starting to emerge.

There is strong evidence for widespread brain changes following Covid-19. SARS-CoV-2 infects the central as well as the peripheral nervous system[10] and the angiotensin converting enzyme 2 (ACE2) receptor at which the virus is thought to act is found in multiple brain regions. Structural MRI data from the UK Biobank cohort found reductions in global brain size, particularly reduced grey matter thickness in the orbitofrontal cortex and parahippocampal gyrus, among participants who had had Covid-19, an average of 141 days before scanning[11]. A significant difference between Covid and non-Covid groups was found in percentage change in performance between assessment periods on the trails B task which particularly taps executive function. This provides evidence that there are physical brain changes post infection that may plausibly underly cognitive impairments. How this occurs is not yet understood.

Brain inflammation resulting from a strong immunological response to Covid-19 is a likely mechanism for many of its neuropsychiatric effects, particularly the cognitive symptoms. Supporting this notion is the fact that the receptor for SARS-CoV-2 (ACE2) is expressed on neurons and glial cells, that SARS-CoV-2 can be detected in the brain, and that astrocytes and microglia cells are activated during Covid-19[12]. SARS-CoV-2 particles spread through the respiratory mucosa and other infected cells, causing changes in peripheral immune cells and eliciting a cascade of immune responses, resulting in a detrimental cytokine storm. A cytokine storm may put Covid-19 survivors at risk for developing long-term neurological/cognitive consequences by either aggravating a pre-existing disorder (eg., Alzheimer's disease), or by initiating a new one. Many cytokine profiles are associated with Covid-19, including tumour necrosis factor-alpha (TNF-α) and a number of interleukins, in particular the rise of interleukin-1β and interleukin-18 which suggests Covid-19 patients may suffer from inflammasome activation[13,14].

Drug development opportunities

Drugs designed to reduce neuroinflammation are currently in development for a variety of brain diseases. These may provide an opportunity for treatment for post-Covid-19 cognitive impairment. However, to invest in drug development for this condition, a number of methodological issues will need to be addressed. In particular, pharma companies and regulators would need to be convinced that cognitive impairment can be reliably measured (first as a diagnostic entity and secondly as an endpoint in clinical trials), and fitted into diagnostic systems and procedural codes, in order to make reimbursement of diagnosis and treatment accessible and commercially viable. Helpfully, much methodology can be borrowed here from the measurement of clinically-meaningful cognitive impairments and changes in older adults, as well as working age people, in disorders ranging from dementia and traumatic brain injury to depression and multiple sclerosis.

Cognitive impairment has been a primary target for regulatory

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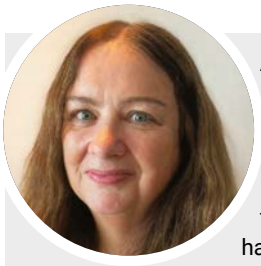
Dr Mark Treherne has been actively involved in the biopharmaceutical industry for over 25 years and previously led the neurodegeneration research group at Pfizer's research facility in Sandwich. To date he has helped to raise over £300 million for early-stage biotechnology companies and out-licensed therapeutic assets for upfront payments, milestones and royalties exceeding £1.5 billion. Treherne is currently Chairperson of Monument Therapeutics. He has a PhD in Pharmacology from the University of Cambridge.



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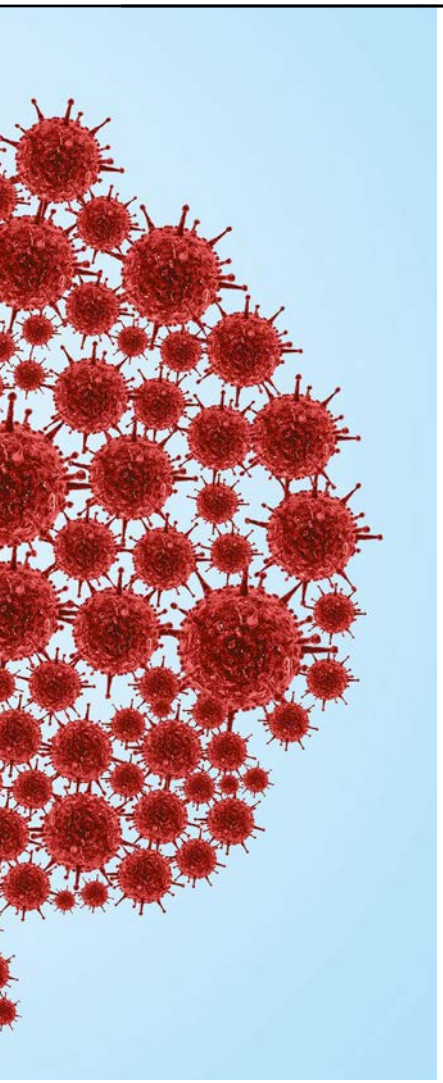
Dr Paula Moran is a pioneering research scientist and an honorary Associate Professor at the University of Nottingham. Following a PhD from the National University of Ireland she has had academic roles at the Institute of Psychiatry, Kings College London and University of Nottingham, where she led collaborations with several pharmaceutical industry partners. She is best known for her translational research on abnormal information processing in both animal and human models.



approvals in several diseases (Alzheimer's, schizophrenia, ADHD) and additional label claims in other (e.g. depression). Regulators are therefore used to seeing cognitive data as primary or secondary outcomes in clinical trials, and are familiar with the instruments and methodological nuances of such data. From an operational perspective, modern cognitive assessment systems are largely digital, minimising the need for trained assessors, and in the context of clinical trials, are increasingly being completed by patients at home via websites or patients' own devices. Diagnostic standards and codes already exist, including the American Psychiatric Association's DSM5 'mild neurocognitive disorder' and ICD 10's 'mild cognitive disorder'.

Given the timescales and resources involved, funders would need convincing that there is a long-term market for a treatment targeting post-Covid-19 cognition. In reality, Covid-19 is nowhere near unique in causing long-term cognitive impairment or 'brain fog'; it has been reported after several other viruses and seems to share phenomenological and biological features with other common conditions that cause disabling levels of cognitive impairment, such as so-called 'chemo brain' (affecting around half of women with breast cancer) and post-operative cognitive decline (affecting around 15% of over-65s after routine surgery). It is likely that these symptoms too are caused by neuroinflammation, thus drugs targeting post-Covid-19 cognitive impairment might well find eventual indication expansions in conditions where neuroinflammation has been triggered by infection, trauma or the side effects of treatments.

A recent study by Castaneda et al[15] in mice was prompted by clinical similarity between post-Covid-19 cognitive impairment and chemotherapy induced cognitive impairment – sometimes called 'chemo brain'. Mild intra-nasal infection with SARS-CoV-2 induced increased inflammatory markers such as cytokines and lower neurogenesis in the brain. This suggests a potential immunological mechanism for how cognitive effects might be happening. Importantly this study raises the possibility that current therapies being developed for chemotherapy cognitive impairment could potentially be applied to Covid-19-related cognitive impairment.

Currently some $200M public research investment mainly from US and UK is being invested in 'long Covid-19' research, with >50% of these studies focused on involvement of the brain[16]. Is it time for the pharmaceutical industry to join in? We believe so.

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Dr Jenny Barnett co-founded Monument Therapeutics and has an MA in Experimental Psychology from Oxford University and a PhD from the University of Cambridge. At Cambridge Cognition, she worked on more than 100 clinical trials utilising cognitive assessments before spinning out Monument Therapeutics, a novel drug development company which uses digital biomarkers to apply a stratified medicine approach to CNS disorders. She has published more than 70 papers, and is an honorary member of the University of Cambridge Department of Psychiatry.

About the author:

Dr Kiri Granger is an internationally-recognised expert in the design of clinical trials for CNS disorders, has provided consultancy to over 50 drug development companies on more than 100 clinical trials and has been the lead scientist on a number of successful programmes. Granger is Chief Scientific Officer at Monument Therapeutics and an Assistant Professor at the University of Nottingham Department of Psychology.