Psychiatric symptoms and cognitive impairment in "Long COVID": the relevance of immunopsychiatry

Although precise estimations of the absolute risk are still difficult to provide, it is clear that depression and anxiety are predominant symptoms in post-acute COVID-19, and that they are more pronounced in patients who have been hospitalized for COVID-19 than in those hospitalized for other respiratory tract infections[1]. Also, cognitive impairment has been reported in several people who have had symptomatic COVID-19 infection, which can manifest as difficulties with concentration, memory, receptive language and/or executive function[1]. Psychiatric symptoms and cognitive impairment can develop and persist months after the infection and are therefore part of what is called the "Long COVID" condition, of which fatigue is another paramount manifestation.

The development of depression and anxiety symptoms and of cognitive impairment after COVID-19 may partly be the result of somatic, functional or psychosocial consequences of the disease. Coronaviruses can also induce cognitive, emotional, neurovegetative and behavioral dysregulation due to direct neurological injury through hypoxic damage and neuroinvasion. In addition to this, the systemic immune activation seen in COVID-19 can contribute significantly to the mental health toll even months after the initial disease.

COVID-19 disease has been characterized as a cytokine release syndrome[2]. Elevated serum concentrations of interleukin-6 and other inflammatory cytokines are hallmarks, and correlate in a dose-response manner with respiratory failure, adverse respiratory distress syndrome, and other clinical outcomes. Immuno-inflammatory dysregulation can contribute importantly to acute and post-acute psychiatric and cognition symptoms in COVID-19 patients.

To illustrate, various lines of research indicate a link between immune activation and depression. First, manipulation of the immune system through endotoxin, interferon-alpha or typhoid vaccine interventions induces sickness behavior involving depressive symptoms such as fatigue, low mood and hypersomnia. Second, large-scale studies confirmed that persons with auto-immune conditions, e.g. rheumatoid arthritis, or with inflammation-inducing conditions, e.g. obesity, have an increased risk to subsequently develop depression. Third, meta-analyses of biomarker studies indicate that levels of inflammatory markers, including cytokines – such as tumor necrosis factor, interleukin-1 beta and interleukin-6 – and acute phase proteins – such as C-reactive protein (CRP) – are significantly elevated in depressed patients compared to healthy controls. Low-grade systemic inflammation has also been shown to induce robust pathophysiological abnormalities in the endocrine systems of stress and arousal regulation that further augment neuroimmune reactivity. In addition, human and animal studies indicate that peripheral immune activation is able to induce brain inflammation, and increased inflammatory responses have been indeed reported in post-mortem brain samples of depressed individuals.

Moreover, large-scale genome-wide DNA and RNA studies indicate that depressed persons have more genetic variants and enriched gene expression pathways involved in immune signaling. Such genetic pleiotropy between immuno-inflammatory dysregulation and depression may indicate a genetic vulnerability that might partly explain why persons with a mood disorder history have a higher risk of unfavorable COVID-19 disease outcomes as compared to persons without a psychiatric history[3]. Finally, anti-inflammatory medication approaches have demonstrated efficacy in reducing depression symptoms.

Of note, findings suggesting a pathophysiological link to the immune system have also been reported for other dimensions relevant to COVID-19, such as cognitive impairment and fatigue. In a population-representative cross-sectional analysis of >40,000 adults, a higher CRP level was associated with poorer executive functioning, which was especially true in the presence of depression and even existed in early adulthood[4]. Longitudinally, high levels of inflammatory markers have been linked to long-term cognitive decline, involving deterioration of memory and executive function[5]. A proteome-wide association study of older-adult brain donors indicated increased inflammation in brains of cognitively impaired persons as compared to those of cognitive stable persons[6].

For fatigue, illustration of immune system involvement comes most strongly from studies of chronic fatigue syndrome (CFS) or myalgic encephalomyelitis (ME), a condition characterized by persistent, unexplained fatigue that is not alleviated by rest. Although CFS/ME has long been indicated as a mystery illness, recent studies suggest that inflammation is central to its pathogenesis in at least a considerable proportion of patients, as suggested by higher levels of inflammatory markers that show a dose-response relationship to disease severity[7].

If even low-grade systemic immune activity increases the risk of depression, cognitive impairment and fatigue, it is obvious that we need to be aware of the role that immune activation can play in the mental health consequences of COVID-19, which involves a massive cytokine storm. A dose-response relationship has been indeed documented between the severity of immune-inflammatory dysregulation in COVID-19 patients and depressive symptomatology three months later[8]. The same study also reported that high baseline inflammation load in COVID-19 patients predicted neurocognitive impairment – involving reduced processing speed, verbal memory and fluency – after three months.

How long the impact of immune activation in COVID-19 patients persists remains to be clarified. However, for infections involving hospital contact, the maximum behavioral effects can take over a year post-infection to fully develop. This suggests that, next to the immediate impact, there may also be priming whereby immune activation triggered by infection (i.e., first hit) may progressively increase sensitivity to common pro-inflammatory stimuli (i.e., second hit), which include other mild infections,

concussions, airborne allergen and pollutant exposure, as well as psychosocial stressors.

Future research goals are to examine how to best monitor, prevent and treat psychiatric, behavioral and cognitive consequences of COVID-19. For clinicians treating depression in patients with SARS-CoV-2 infection, a thorough history and clinical examination are paramount. There is evidence that immune-inflammatory dysregulation is limiting the efficacy of antidepressants, as high plasma levels of CRP and interleukins have been found to be predictors of poor treatment response[9]. Consequently, whether antidepressants are effective in treating COVID-19-related depression deserves specific confirmation.

In the meantime, we can assume that any major advances in vaccines and antiviral treatments targeting SARS-CoV-2, as well as immune targeted therapies (such as anti-cytokines and cytokine receptor blockers), will not only prevent severe illness but also benefit the brain and mental health.

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Learning from the global response to COVID-19 to accelerate innovation in mental health trials

The past two decades have seen an increasing recognition of the contribution of mental disorders to global disease burden. There has also been an awareness that therapeutic innovation based on sound understanding of disease mechanisms has evaded single companies working within a conventional competitive market-based model. Governments, charities and philanthropists are increasingly willing to fund research programmes, and several collaborative initiatives and networks have emerged in recent years. For example, we soon expect the launch of the Health Brains Global Initiative (https://www.hbgi.org), which aims to "address market failures by galvanizing new science and new finance to enable new life trajectories".

Those of us involved in brain health research have a responsibility to take this opportunity, but we need to identify clear objectives and priorities to ensure that we deliver real advances. Inspiration and exemplars can be drawn from many areas of collaborative science. An example is the global response to the COVID-19 pandemic, where, alongside the dreadful death toll and enormous human suffering, we have observed the extraordinary acceleration in research success that is possible when researchers and funders collaborate with shared purpose, and prioritize and coordinate their efforts.

The extraordinary response to COVID-19 has not emerged out of the blue. The global research community had learned from previous inadequate responses to infectious disease outbreaks and created the partnerships and platforms to ensure a state of preparedness for emerging epidemics. The International Severe Acute Respiratory and emerging Infection Consortium (https://isaric.tghn.org) was funded in 2011 to ensure a rapid clinical research response to epidemics. The Coalition for Epidemic Preparedness Innovations (https://cepi.net) was launched in 2017 with a mission to "stimulate and accelerate the development of vaccines against emerging infectious diseases and enable access to these vaccines for people during outbreaks".

What are the key areas in trial design and conduct that have delivered the vaccines? A key area has been the standardization of early phase clinical trials. Vaccine development is not alone here – the critical contribution of phase II trials in providing crucial go-no-go evidence at earlier phases of development (rather than waiting to discover lack of efficacy in highly costly phase III trials) has been recognized for almost two decades[1]. This is most effective when illness mechanism is understood and biomarkers/interim outcomes can be reliably linked to clinical outcomes. Hence, phase II vaccine trials assess immune response rather than clinical outcomes[2].

Pathogenetic understanding of mental disorders is still limited, but the tactic of reverse translation, investigating the effects of treatments of known efficacy on biomarkers, has been productive. For example, antidepressant drugs have rapid effects on emotional bias, and this is a useful experimental measure of potential longer-term therapeutic effect[3]. Emotional bias is now used frequently in early phase studies as an indicator of longer-term clinical benefit of putative antidepressants.

An additional striking feature of the COVID-19 vaccine development has been the disruption of the standard linear sequential approach. Phase II/III trials have been planned and set up – using efficient combination designs – while preliminary studies were just getting underway. We have previously suggested that a non-linear, iterative approach might also be of benefit in drug development in psychiatry[4].

The COVID-19 pandemic also provides an excellent example of the power of embedding a highly simplified, randomized trial platform comparing available and licensed medicines in real world settings. The RECOVERY trial was rapidly designed and set up in March 2020[5]. It randomized over 35,000 patients by February 2021. By that time, it had demonstrated the benefits of dexamethasone