

Responses to Participants' Questions

This document provides responses* to questions raised by webinar participants related to the following presentations:

- **Presentation 1: *Psychiatric Symptoms in Coronavirus Illnesses: Prior Outbreaks and Early Questions for Long-Term COVID-19 (PASC) in Pediatric Samples***
Richard Gallagher, PhD
- **Presentation 2: *Prevalence and Characteristics of Long COVID in the US***
Roy Perlis, MD, MSc
- **Presentation 3: *Short- and Long-Term Effects of COVID on Brain and Mental Health***
J. Douglas Bremner, MD
- **Discussant: Naomi M. Simon, MD, MSc**

* Responses may have been edited for clarity.

All Presenters: Questions and Responses

Q. What do you feel are the greatest lessons learned and the greatest opportunities for better understanding mechanisms and treatments of PASC?

Responses:

Dr. Perlis: I'm concerned that one of the big gaps in our knowledge is the strain specificity, or the variant specificity, of some of these effects. I think we've learned a lot about the persistence of symptoms and the nature of those symptoms. As Dr. Gallagher pointed out, I think we're starting to get to mechanisms. There's a convergence of some of the imaging work, some of the neuropsychiatric work, and some of the cellular modeling, although the cellular modeling so far is very early. So, we're starting to get to mechanisms, but I worry that we have this snapshot blurred over what are essentially very different viruses, at least in terms of their potential brain effects. I'm hopeful that we'll start to understand this better when we have longer follow-up from the era when there are all of these newer variants to contend with.

Dr. Bremner: In my review to prepare for this talk, I saw that in the search for COVID in the brain, over 6,000 papers have been written in the past 2 years. It's quite remarkable and I've never seen anything like this in terms of the volume of what's been written. Probably a third of these papers are speculative meta-analyses, case series reviews, and "this is our perspective from XYZ country with 60 patients." I found a couple of striking parallels to

another area that I've been involved in in the past, the acne medication called isotretinoin (Accutane). There's the question whether it causes depression or suicide, and you get a number of these studies with a sample size of 60. I don't think that kind of research moves the bar forward. So, I appreciate your perspective on the chart review.

One of the questions that came up is, are these studies leading to answers that are biased or otherwise not providing better information? One review paper found similarities between Long COVID and the long-term effects of isotretinoin, as well as overlap with chronic fatigue syndrome and other chronic inflammatory conditions. One of the threads is brain fog, a symptom that a lot of physicians may have ignored in the past. But it is something that patients complain about and we need to pay attention to it. So, looking at the other syndromes, there's brain fog, cognitive impairment, and sexual dysfunction, which is another PASC symptom that has not been highlighted but is seen in some of these other long-term syndromes. So, one paper was saying maybe PASC is causing an increase in vascular damage to the liver and causing a massive release of retinoids in the blood system, which is another possible mechanism that people haven't thought about. Retinoids affect transcription. Vitamin A is a retinoid and high levels of vitamin A can cause psychosis and neuropsychiatric symptoms, so that's another possible mechanism.

A key area to hone in on is the mechanism: Is this an inflammatory response? Is there an invasion of the neurons by the virus? Is this a secondary effect of the vascular inflammatory response causing damage to neurons in the brain?

Q. Have you seen any incidence of obsessive compulsive disorder following a COVID infection in adults or in children?

Responses:

Dr. Bremner: There are two studies showing an increase in obsessive compulsive disorder following COVID infection:

- Mazza MG, Palladini M, De Lorenzo R, et al. Persistent psychopathology and neurocognitive impairment in COVID-19 survivors: Effect of inflammatory biomarkers at three-month follow-up. *Brain Behav Immun.* 2021;94:138-147. doi: [10.1016/j.bbi.2021.02.021](https://doi.org/10.1016/j.bbi.2021.02.021)
- Mazza MG, De Lorenzo R, Conte C, et al. Anxiety and depression in COVID-19 survivors: Role of inflammatory and clinical predictors. *Brain Behav Immun.* 2020;89:594-600. doi: [10.1016/j.bbi.2020.07.037](https://doi.org/10.1016/j.bbi.2020.07.037)

Q. Please provide any information regarding federal funding for Long COVID clinics to ensure there is a mental health provider as a requirement for funding. If there is no such requirement, why not?

Responses:

Dr. Bremner: There is an initiative to get additional funds from Congress for the RECOVER centers to provide treatment for Long COVID. Speaking for the members of the RECOVER Neuropsychiatry Committee, we will certainly advocate for mental health resources as part of that.

Q. How does mitochondrial dysfunction fit into the mental health continuum? Are you testing for this?

Responses:

Dr. Perlis: The best answer to date is that we have no idea. We don't really understand mitochondrial dysfunction well in psychiatric disease and only in a subset of neurologic diseases. Certainly, it's something people are looking at. For example, those of us who do cellular modeling characterize mitochondrial function as part of what we do, but anyone who says they understand whether and how mitochondria continue to contribute to Long COVID is probably going beyond the current data, at least that I've seen.

Q. When there are patients that have rare symptoms such as psychosis, is there a national collection of data that Long COVID clinics can report information to so that it is gathered and analyzed in one central point as opposed to one patient here or there?

Responses:

Dr. Bremner: We do have screening questions for psychosis that trigger a full diagnostic interview for psychotic disorders. All these data go into the central RECOVER database.

Q. Are you finding more women than men are presenting with Long COVID memory issues? And are you finding more women than men presenting with memory issues who had the ancestral COVID, the Omicron variant (all forms), or the Delta variant?

Responses:

Dr. Perlis: I can answer that based on our survey, as we absolutely see substantially more cognitive symptoms among women compared with men. So, conditional on having Long COVID or saying you have persistent symptoms, we do see more cognitive symptoms in women than in men, but we don't understand why that might be. Regarding variant-specific effects, we're certainly looking at it but we simply don't yet have enough data to weigh in on that.

Q. Given dysautonomia is a well-established comorbidity of post-acute sequelae to infectious illness, and that dysautonomia has direct physiologic impact on cognitive function and anxiety, have these investigators considered using self-administered NASA Lean Tests in these mental health studies (heart rate measurements lying, sitting, standing) to assess dysautonomia as a physiologic underpinning to the ascertained mental health diagnoses?

Responses:

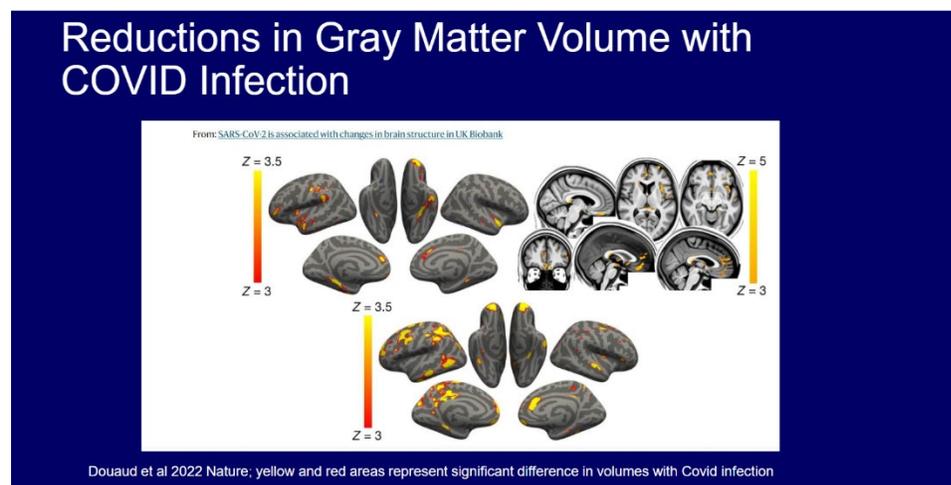
Dr. Bremner: We've collaborated with Bashar Badran and colleagues on a study in which they were testing vagus nerve stimulation on Long COVID patients.¹ Also, they were coupling that with wearable sensing devices, so they were teaching people how to put on these devices that would measure various aspects of autonomic function, and then they're able to collect the data in real time as they administer treatment. With dysautonomia, it's probably the brain that causes the dysregulation of peripheral autonomic function.

Dr. Simon: I would point out that the RECOVER Neuropsychiatric Committee has been reviewing the different standard operating procedures and plans, and there is a focus on autonomic dysfunction that is part of RECOVER.

Q. Are all the FDG-PET (fluorodeoxyglucose) scans before and after COVID, or can Long COVID-induced psychiatric symptoms be identified by lower than "typical" values to normal?

Responses:

Dr. Bremner: Many Long COVID studies are looking at before infection/baseline, 1 month, and 6 months for positive cases as compared with controls. Some studies are looking at people with the diagnosis of Long COVID syndrome and comparing them to normal databases. We do see brains that have bright yellow areas showing where there are differences, and those are significant differences for these intervals.² The figure below depicts reductions in gray matter volume with COVID infection (used with permission).



Q. Do we know how permanent these brain changes may be?

Responses:

Dr. Bremner: We're still within 2 years of the pandemic, consequently long-term brain effects are not known.

Q. Dr. Bremner, is the severity of the acute phase of COVID related to the brain damage? Or can asymptomatic people have internal damage, as shown in the brain image?

Responses:

Dr. Bremner: We don't have any evidence that nonsymptomatic COVID is associated with brain changes. So far, it appears that people with more severe COVID symptoms have more brain changes.

Q. Dr. Bremner, is neuromodulation similar or the same as neurofeedback therapy?

Responses:

Dr. Bremner: Neuromodulation is delivery of electrical or magnetic pulses to the brain or cranial nerves that have input to the brain and it's not necessarily paired with anything, whereas neurofeedback involves the person viewing a brain or cardiac signal and modifying it through their behavior. We've done studies on neurofeedback and it's a useful tool for some conditions. What hasn't been done yet would be to use magnetic pulses (transcranial magnetic stimulation). All of these deliver some type of external impulse.

Q. Do you know if there is any longitudinal data on multiple COVID-19 infections on PASC neurological symptom prevalence?

Responses:

Dr. Simon: I haven't seen anything in the literature that has addressed that.

Dr. Perlis: I also haven't. It's a very difficult thing to study given the designs that have been applied so far. It's a critical question as we accumulate multiple infections, but for a lot of the reasons I mentioned regarding electronic health record limitations, it's not trivial to capture that kind of exposure.

Dr. Simon: Yes, and it's even harder now with a lot of home testing. But hopefully with some of the interviews and the 3-month follow-ups in the prospective sample, we'll capture some of that in RECOVER.

Dr. Perlis: It's interesting hearing all these different perspectives about what we do know about Long COVID. It makes a study like RECOVER that much more critical because it fills the gap between these other kinds of approaches.

Q. How do reported Long COVID depression, anxiety, and other mental health symptoms in the US compare with other Western countries?

Responses:

Dr. Bremner: I'm not aware of any such studies.

Q. Are you finding studies considering the impact of post-COVID hormonal changes on mood and cognitive issues?

Responses:

Dr. Bremner: I'm not aware of any such studies.

Q. Is there any evidence for cognitive therapy helping memory issues?

Response:

Dr. Bremner: I'm not aware of any such studies.

Q. Have there been any studies that include patients with prior traumatic brain injury and increased cognitive impairments post-COVID?

Responses:

Dr. Bremner: I'm not aware of any such studies.

Q. Does any of the research show why depression and panic attacks are so prevalent in COVID long haulers?

Responses:

Dr. Bremner: One of the goals of the RECOVER study is to determine to what extent anxiety and depression are related to the stress of the aftermath of severe illness and how much may be related to COVID-related brain changes.

To Learn More

- Information about RECOVER research and to volunteer for studies: <https://recovercovid.org/research>
- Frequently Asked Questions about RECOVER and PASC: <https://recovercovid.org/faqs>
- CDC information: Information for the general public and for healthcare providers about post-COVID conditions: <https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/>

References

1. Badran BW, Huffman SM, Dancy M, et al. A pilot randomized controlled trial of supervised, at-home, self-administered transcutaneous auricular vagus nerve stimulation (taVNS) to manage long COVID symptoms. Res Sq [Preprint]. 2022 Jun 21:rs.3.rs-1716096. doi: [10.21203/rs.3.rs-1716096/v1](https://doi.org/10.21203/rs.3.rs-1716096/v1)
2. Douaud G, Lee S, Alfaro-Almagro F, et al. SARS-CoV-2 is associated with changes in brain structure in UK Biobank. Nature. 2022;604(7907):697-707. <https://doi.org/10.1038/s41586-022-04569-5>