Transcript

Lisa Newman

I'm Lisa Newman, Project Director for RECOVER at the Administrative Coordinating Center at RTI International and the moderator of today's webinar. Welcome to the RECOVER Research Review or R3 webinar. The goal of this webinar series is to catalyze the formation of a scientific stakeholder community within and beyond the RECOVER consortium and foster a shared understanding of the state of the science, and also to provide an enduring educational resource for RECOVER investigators, the broader scientific community, clinicians, patients, and other public stakeholders.

I want to thank everyone who submitted questions in advance. Please submit any questions that arise today using the Q&A feature in Zoom, as Shane mentioned. After the presentation, we will answer as many questions about today's topic and presentations, as we're able. Some questions may also be answered immediately within the Q&A. We also encourage you afterwards to go to the FAQs on our website, recovercovid.org, and you can see that on the screen, where we will post answers to questions we may not be able to get to today.

We have an impressive panel of speakers. Our speakers will discuss what is known about the effects of COVID on pediatric and adult mental health and brain changes in mental health issues caused by COVID. Our presenters today are Dr. Richard Gallagher, Dr. Roy Perlis, and Dr. Doug Bremner. Dr. Naomi Simon will synthesize the information presented by the panelists and guide subsequent discussion with them.

First, Dr. Gallagher is a Psychologist and Associate Professor of Child and Adolescent Psychiatry at the Child Study Center at the NYU School of Medicine. He specializes in the neuropsychological assessment and treatment of anxiety disorders, attention deficit hyperactivity disorders, and learning disorders. He has been a co-principal investigator on National Institute's of Mental Health grants that investigate executive function deficits in children with ADHD and related disorders, and how to overcome those deficits through training.

Dr. Roy Perlis is Associate Chief for Research in the Department of Psychiatry and Director of the Center for Quantitative Health at Massachusetts General Hospital. He is a Professor of Psychiatry at Harvard Medical School. Dr. Perlis' research is focused on identifying predictors of treatment response and brain diseases and applying these biomarkers to develop novel treatments. His laboratory identified the first risk genes for major depressive disorder and led the first genome-wide association studies of lithium response, as well as suicide risk. More recently, they identified the first patient-derived cellular model of schizophrenia liability.

Dr. Doug Bremner is a Professor of Psychiatry and Radiology and Director of the Emory Clinical Neuroscience Research Unit at Emory University School of Medicine in Atlanta. He is also a Chief Psychiatrist at the Atlanta BA Medical Center. Dr. Bremner's research has used neuroimaging and neurobiology measures to study the neuro-correlates and neurobiology of post traumatic stress disorder related to combat and childhood abuse

and related areas of depression. His more recent work looks at the relationship between brain behavior and physical health, including studies of neurobiological mechanisms involved in the relationships between stress and depression and cardiovascular disease, as well as the effects of different treatments for stress-related conditions on the brain.

Finally, Dr. Simon is Professor of Psychiatry at NYU Grossman School of Medicine and Director of the Anxiety, Stress and Prolonged Grief program. And she's also a senior advisor to NYU's Steven Cohen Military Family Clinic. She has over 20 years experience conducting clinical and translational research in anxiety disorders, prolonged grief and stress related disorders. She is the lead editor of the new American Psychiatric Association textbook of Anxiety, Trauma, and OCD Related Disorders, and has mentored scores of graduate students, residents, post-doctoral fellows, and junior faculty in clinical and translational research.

Just a quick note before we get started, Dr. Gallagher needs to leave soon after his presentation today. Following his talk, if they're relevant question, I'll pose a question or two, then we will continue with the presentations by doctors Perlis and Bremner. Following their presentation, Dr. Simon, our discussant, will conclude by synthesizing the presentation, asking a few questions to start the discussion, and then we will open it up to questions from the audience. Please welcome all of our speakers. Now I will turn it over to Dr. Gallagher.

Dr. Richard Gallagher

Thank you. So, let's please start with these slides and have us work in that direction, please. And the psychiatric symptoms in coronavirus illness, we're going to talk about them based upon some prior outbreaks of different forms of viral infections, and then some of the early questions for long-term COVID-19 in pediatric samples. The next slide, please.

The psychiatric symptoms in RECOVER are going to be reviewed in RECOVER in all of the cohorts, it's going to be in the adult cohort and then in several sections of the pediatric cohorts. In the pediatric cohorts, there is going to be an evaluation of both caregivers and children in the main cohort, incorporating 6,000 children that have been exposed or not exposed to COVID and who demonstrate either long COVID or do not demonstrate long COVID. There is a group of children that are being evaluated, whose mothers were exposed or not exposed during pregnancy in this time period. And there's 2,500 children that are going to be evaluated in that fashion.

And then there is a group of children in the multisystemic complications that have been present, and that will be a group of children that will be evaluated for demonstrating those problems, as well as some control children that do not demonstrate that post-vaccination. And then finally, there's a large scale study that is the Adolescent Brain Development Study that is really reviewing a great number of adolescents to see the nature of adolescent brain development during the teenage years. And those will be children that were also evaluated for their psychiatric symptoms and their exposure to COVID. Next slide, please.

There are a myriad of psychiatric concerns that are present, that we need to be taking into account. There's certainly the consequences of COVID exposure and the resulting illness. And there are indications of post-traumatic stress disorder or symptoms for a number of people that have had pretty serious complications and treatments that have really required a lot of stress and responsive stress. Then there's also been concerns with regard to the psychiatric reactions to changes in functioning, especially for persons that have long COVID, that may be change in their level of fatigue, changing in their sleeping patterns, changing in a number of other issues that are being assessed and being reported in persons with long COVID.

Additionally, there's the consequences of the illness affecting others. There's a number of persons that unfortunately will be having grief reactions to loss of family members and friends. There's also been an increased stress for others in caring for people that have had COVID. And that is another issue that could be contributing to some psychiatric outcomes for people all around.

Finally, there's the consequences of public health responses to the outbreak in both COVID exposed persons, as well as controls. There's certainly psychiatric responses that could be present because of increased isolation. There's responses to the increased in general societal anxiety. And then there are responses that can also be present for persons because of their changes in their economic status, because of the responses and the things that have had to happen because of COVID. And then, there is speculation about the potential direct central nervous system impacts of the virus in the brain.

And let's talk about the next slide. The next slide shows three proposed pathways to impact on the central nervous system. One is that the COVID virus itself may cross the blood-brain barrier through the ACE3 receptors that are present in nerve cells, as well as many other cells throughout the body. And this is the angiotensin-converting enzyme number three, which the spikes of the COVID virus actually connect to and get into these cells.

There's also an issue because of the propensity for COVID to be in the upper respiratory system that it could pass through the cribriform plate near the olfactory bulbs. And this is at the top and roof of the mouth where the olfactory nerves come down for our senses of smell. And it's believed that the COVID virus may be able to pass into those nerve tissues and then get into the central nervous system.

And finally, there's a possibility that the disease process may cause systemic inflammation, which may include inflammation in the central nervous system and causing changes in the functioning of those neurons. These are speculations, they're not confirmed, but there are pretty serious considerations that these are ways that the virus may get directly into the brain. Next slide please.

And so, that we have a myriad of psychiatric concerns with, at the end of this kind of equation, being the psychiatric symptoms that are possible. There's certainly COVID exposure. Then there's treatment experiences that can result in some issues as people are going through treatment and even though treatment is working to be able to help people out, there are some treatment experiences that as people are in the hospital or in other situations, that can actually contribute to their anxiety and reactions. There is changes in their neurological functioning and

also changes in person's quality of life that can have an effect. And there are issues that have to do with the exposure to the quarantines and then changes in the way that life is being handled altogether. So, again, multiple, multiple possibilities. Next slide, please.

And in summary, with regard to the research that's been done on adults, and this is clearly in a more advanced stage than it is for pediatrics at this time, based upon prior research in adults conducted through some meta analyses and other summaries, anxiety is likely to be prevalent perhaps only in the first months following COVID exposure. Also, depression is likely to be prevalent with indications that it can be persistent. For adults, there's PTSD symptoms that include anxiety and depression that are likely to be prevalent, especially in those that were hospitalized and those that required intensive care unit treatment.

Psychosis is relatively rare, however, it has been reported at higher rates than under typical circumstances comparing post-COVID to pre-COVID. And the mechanisms for change, again, are not well understood. Again, we do talk about these candidates includes increased inflammation of CNS tissue, and again, there's these ideas that COVID-19 may be neurotoxic, but it's not completely clear about that.

And what's important is that comparing to control groups with limited exposure to COVID is really critical because in the adult literature, and as we soon find out in the pediatric literature, the background responses to COVID has resulted in significant increases in psychiatric symptoms in the population in general. Next slide.

So, suggestions from precursor illnesses are playing a part with regard to understanding issues in the pediatric population. We can talk about the 1918 Spanish flu, which was a worldwide pandemic that lasted for five years with several waves, but also overlapped it with a pandemic of Encephalitis Lethargica, which started in 1917. And indications are from looking at things historically, that both of these pandemics were associated with significant changes in the psychiatric patterns of kids that were exposed to these. In fact, the idea about what's been described as minimal brain damage and the ideas that kids could be influenced by their environment and illnesses that they get, that would result in hyperactivity, impulsivity, and some problems with attention, does come from this work looking at the Spanish flu and the Encephalitis Lethargica.

HIV has been studied extensively. It's been found not to have a lot of importance with regard to this outbreak, because it's a different kind of virus. However, these shared respiratory infections that we're seeing in SARS, COVID 1, and MERS, has been found that these issues have been something that has resulted in increases in psychiatric concerns. And then, H1N1 has also been of concern as well. Next slide, please.

And these are some of the issues that have suggestions from these illnesses. From the 1918 influenza and Encephalitis Lethargica, there's been neurological complications that did last. They were proposed to be associated with inattention and hyperactivity as the proposed source of what's been described as minimal brain dysfunction. Both SARS and MERS are both coronaviruses and what's been studied in terms of looking at the neurological complications in pediatric samples, rather extensive reviews have indicated that six of seven coronaviruses that have been studied did include significant neurological complications in pediatric samples. And these complications

are quite serious, they have included encephalitis, persistent motor weakness, and behavior change noted, and this is documented and reviewed by a study by Singer et al. Next slide. Next slide, please. Thank you.

And these are samples of information that's been found with regard to this pediatric psychiatric, emotional, and behavioral patterns, that is in the background. These are symptoms that have increased in response to COVID-19 and its broad impact. So, these are population studies that have been done and reviewed in summary studies that include one by Jones et al. that looked at studies that were reported throughout the literature that involved 40,000 subjects in 16 studies with adolescents. And compared to the pre-COVID time period, the population in general, around the world, these are samples from around the world, including the United States, that there has been an increase in anxiety, an increase in depression, and an increase of substance use, including alcohol and marijuana use. And this is again in the population in general.

Samji et al. also looked at 116 papers that included 127,000 subjects. And they reported in their samples that in order of significance, the population in general, and this is with kids as well as adolescents, that there's been an increase in fear of COVID itself. There's been an increase in depression, an increase in anxiety. There's actually been an increase in also non-suicidal self-injury and an increase in suicidal ideation. And Meade, in another summary, has found that there's been increases in anxiety and depression compared to pre-COVID times. So, in the background, we have a lot of indications that the pandemic has had a significant impact upon adolescent and child mental health. Next slide, please.

And what's also been found in the acute illness phase is that this is considered to be in the four months after COVID exposure for kids, that there's been an increase in fatigue in the pediatric population. There's been an increase in sleep disturbances. There's been an increase in attention problems, and there's been an increase in anxiety. So, this is what we know with regard to COVID exposure in general. And this is in relation to control groups, kids from the backgrounds that have not been exposed to COVID itself. Next slide.

And when we do talk about pediatric psychiatric emotional behavioral patterns in long COVID, there's only been two really large studies that have been reported so far. Borch et al. in the study that was done nationwide in Denmark and looked at the really large sample of persons that responded to online requests to respond. 37,000 positive COVID cases that had PCR confirmation of COVID did respond. 78,000 of kids with negative COVID cases with negative PCR tests, were considered to be the control group. What was interesting about this, which is really important for RECOVER and the future, is that many controls talk about persistent similar symptoms for four months or more, but the positive COVID group did report an increase of 0.8% in persistent physical and mental health symptoms.

In general, when we talk about the kids with PASC or long COVID, 12 to 51% of the kids reported persistence of symptoms after four weeks. But again, interestingly, the control group report persistence of symptoms that they said are things that have lasted with them for more than four weeks, even though they haven't been exposed. The mental health related symptoms include the following. For the kids with COVID

exposure, it has been fatigue and dizziness. And with kids in the non-COVID exposed group, they've had concentration problems and headaches. Next slide.

Another sample reported was a systematic review and meta analysis of 21 studies with 80,000 subjects. There were only a few of these with studies. And the top three persistent symptoms impact mental health directly are, 16% report mood problems, 10% report fatigue problems, 8% report sleep problems. And then cognition ranked number seven with regard to concentration was reported by 6% of these persons. Next slide.

And in terms of research and clinical considerations, these are the ideas that come across. It's important to understand the prior developmental course of the subjects. It's really important to understand the exact COVID status, especially within pediatrics, many kids were asymptomatic and continue to show that way, but have been exposed to COVID. And we need to understand the impact because of these background issues of the COVID response environment. There's been altered social contacts, there's been very different altered educational delivery. There's been altered family interactions. And there's been the direct and indirect impact of loss of life and serious illness in others. Next slide.

And we want to be able to think about these things as being of concern at different age ranges. And this is recommended by Singer et al. kids between zero and three, there might have increased irritability, outbursts and changes in sleep. Kids between three and six, the possibilities are issues with emotional deregulation, hyperactivity, impulsivity, and also changes in sleep. And for persons between six and 18, there's a concern about the addition of depression and anxiety, as well as the others. In terms of the data that's being collected in RECOVER, at tier one there's screening of parents and children through questionnaires. In tier two there's interview questions through in-person contacts and uses of comprehensive rating scales for looking at anxiety, depression, and behavior changes. And then in tier three, there's a structured diagnostic interview, plus these rating scales done twice. So, there's a good follow-up review. Next slide, please.

And these are the kinds of questions that are being asked in RECOVER. What are the higher frequency symptoms among long-term COVID subjects? How do these frequencies compare to background symptoms? And what factors contribute to heightened symptoms? What factors can be linked to evidence of CNS physical changes? What symptoms can be linked to illness experience? What symptoms are linked to diminishing functioning? And what symptoms are linked to COVID restrictions? Finally, what symptoms can be linked to grief and stress, and does bodily response to the illness also contribute to symptom frequency and pattern? And next slide, please. So, thank you, and I'm happy to take a few questions if they're available, and thanks for paying attention.

Lisa Newman

Dr. Gallagher, thank you for a fascinating presentation. There is a question specifically for you. How do you know the not exposed groups have not been exposed, given the underreporting of COVID-19 cases?

Dr. Richard Gallagher

Well, what's going to be done with the extensive evaluation that occurs moreso in tier two and tier three, is that the children will be evaluated and looked at with regard to samples of their nasal tissue and other blood studies that are being done to look to see if it's present, even though the kids may have been asymptomatic and don't know that they had COVID.

Lisa Newman

And how about one more, Dr. Gallagher, before you leave?

Dr. Richard Gallagher

Yes.

Lisa Newman

Have you seen any incidence of OCD following a COVID infection in children?

Dr. Richard Gallagher

Well, again, we have to think about things with regard to background. Many kids that have had issues with obsessive compulsive disorder beforehand did have it exaggerated during COVID, especially with all the concerns about hand washing and making sure that you protect yourself from germs. I have not personally seen that, but that is something that is being reviewed. It is one of the questions that are being asked of people in these different levels of study.

Lisa Newman

Thank you, Dr. Gallagher, we'll let you go and carry on with our presentations.

Dr. Richard Gallagher

Thank you.

Lisa Newman

Appreciate it. Okay, Dr. Perlis, onto you.

Dr. Roy Perlis

It's a pleasure to be here today. And actually, I think, pick up where Dr. Gallagher left off in nicely framing some of the prior work that's been done to understand long COVID and some of the different perspectives. I want to talk generally about what we know about prevalence of long COVID and then focus in a little bit and talk about our own work, trying to understand CNS symptoms and in particular, how prevalent individual symptoms might be.

Just to put everything in context. If you go back a little more than two years, we really thought that this was a conversation that would be confined to other countries and other settings, but really as far back as spring of 2020, it started to become apparent that we would have to contend not just with the acute symptoms of the virus, but potentially with longer-term neuropsychiatric symptoms as well. So, we've learned a lot in the past two-plus years, and I want to start by talking a little bit about what the context has been, what are the ways that we might approach this kind of knowledge?

So, when we think about understanding long COVID, we might just take a cross-sectional design, right? We might go out, recruit a bunch of people or evaluate a bunch of people after hospitalization, or in an ICU, or in a rehab unit. We might learn something that way about current symptoms, current state. We might instead enroll a bunch of people and look backwards as is part of what's been incorporated in the RECOVER design. So, asking a past history, or we might enroll a very large cohort and follow them forward and do prospective assessment. And that too is part of RECOVER. And all of those approaches have their various strengths and limitations, in particular what's feasible.

So, early in COVID, I think there was a lot of cross-sectional assessment, a lot of retrospective assessment as we move towards being able to stand up these longer term studies. So, one dimension to think about is how are we following people over time? The other is, how are we measuring symptoms? And that gets to be really important when we're thinking about long COVID, because how we define it and how we measure symptoms is going to have a big impact on the prevalences that we identify and the symptoms that we associate with long COVID.

So, again, early in the course of the pandemic, a lot of the published work focused on things like chart review. So, these are the first 20 people in our ICU, or these are the first 20 people who presented with positive tests. More recently, that's been scaled up dramatically with studies that use electronic health records, or registries, or administrative claims data. I'm going to talk a little bit about that in a moment.

And now we're seeing more efforts at systematic phenotyping, so perhaps piggybacking on that kind of ascertainment, we can then go back and do additional neuropsych testing, additional rating scales, additional physiologic assessments. Complementing these kinds of approaches have been approaches again, alluded to by Dr.

Gallagher, that use things like apps or surveys to go out, often outside of a clinical setting. So, not just asking about people in a particular clinic or people discharged from the hospital, but sampling more broadly to say, "Do you have symptoms? What kinds of symptoms do you have? How long have you had these symptoms?" Each of these approaches to methodology or each of these kinds of methodology, have their own strengths and their own challenges. And in particular, when you change the sampling frame, you're going to get very different estimates of prevalence. And I think that's why, at least so far, when people talk about long COVID, you hear numbers from fractions of 1%, all the way up to a quarter of the population. And it really depends on how you're measuring and how you're defining.

So, I'm going to start by talking just a bit about our work with electronic health records and claims data and then I'm going to pivot and talk about a survey called the COVID States Project, which has been a major focus of myself and my collaborators over the last two-plus years. And in so doing, again, try to put a little bit more gloss on how different methods give you different estimates.

When you look at an electronic health record study or an administrative claims study, I think it's really critical to ask a few questions about where these data come from and what they mean. So, can you reliably measure the exposure? Do we know who had COVID? Do we know who had a positive test? That tends to be pretty good in electronic health records, or at least was, until we started shifting so much towards antigen-based testing that doesn't necessarily get recorded. Can you reliably measure the outcome? That I think is where EHR and administrative data for long COVID really falls short. And I'm going to show you why I think that in just a minute. So, how do you measure long COVID?

What does it mean to be missing? In other words, who are these people in my electronic health record? Are they representative of the general population? Are they just people with insurance? Are they just people with particular kinds of insurance? I think if we want reliable estimates, we have to grapple with those kinds of problems. And then of course, what are the confounding variables? What else goes either with the exposure and the outcome that might give me misleading results? This really applies to any kind of EHR study.

I want to drill down and talk specifically about outcome. So, this is from a paper we published earlier this year in Molecular Psychiatry, where we used the electronic health records of the Mass General Brigham health system to try to get a handle on long COVID symptoms or persisting COVID symptoms after an inpatient hospitalization. And I would say the good news is EHR data are free or nearly free, we get massive amounts of data very efficiently, which is why it was such an appealing approach early in COVID. Problem is, you get what you pay for, which is to say the quality of the data in terms of its ability to capture diagnoses, particularly when those diagnoses are not yet well defined and they're still evolving, can be highly variable. Right?

So, remember, it was nearly a year until we had a diagnostic code for long COVID, and even now it's not necessarily consistently applied. So, what we tried to do in this study looking at long COVID symptoms was say, if we pick a few symptoms, say, anosmia, headache, fatigue, and we look at how reliably they're captured in claims

codes, in ICD 10 codes, how reliably they're captured with natural language processing, and then how reliably they're captured when we compare them to a gold standard, what do we find? Right? So, what's the best way, if I'm approaching one of these large data sets, to understand what the true prevalence of a symptom might be?

And the notable finding from this table, which we actually buried in supplemental materials, because it seemed mostly interesting to us, but in hindsight, probably pretty important in thinking about long COVID, the take home is that neither the claims codes nor fancy natural language processing is really especially reliable, especially in terms of sensitivity for identifying potential long COVID symptoms.

Okay. So, it's really hard to look at an EHR and say, "This person has long COVID." And I think that's a challenge in any sort of estimates that use this kind of approach and try to define outcomes. So, for example, when we apply our own method, which uses both natural language processing and claims code, to a large cohort of people hospitalized in our health system, and compare those who did or did not have a positive COVID test, you see a couple of things. Consistent with what Dr. Gallagher said, you see high rates of things like fatigue, cognitive complaints, insomnia, but you see high rates both in those hospitalized for COVID and those hospitalized for something else.

Now, the point is not that there's not such a thing as long COVID, there's abundant data that there is. The point is that our approach to capturing it in electronic health records may not really give us particularly reliable or particularly useful estimates, because what we find is for many of these symptoms, they're equally common in people hospitalized for COVID or for some other diagnosis, okay? Kind of a, I think, critical point.

So, because of the challenges in looking at long COVID solely using electronic health records, we have subsequently shifted a lot of our work to build on a collaboration between my group and colleagues at Northeastern and at Northwestern and Rutgers, and elsewhere, that fields a very large survey across the United States about every six to eight weeks. And this is called the COVID States Project. The website is on the slide. A lot of what we do has to do with COVID behaviors, COVID attitudes. It's not specifically a study of long COVID or neuropsychiatric symptoms in long COVID, although, as you will see, we've found ways to apply it that way.

Just to give you a little bit more background, we survey over internet in all 50 states and the District of Columbia, we collect about 20,000 adult or 18 and older participants, every six to eight weeks. We started in spring of 2020 and we've been going since then. We're about to launch wave 24 in a few weeks. The participants in the study are drawn from online panels who can opt in to a survey. This is a critical aspect of the COVID States Project, it is portrayed as a survey of people's behaviors and opinions. It is not portrayed in particular as a COVID survey. So, we ask about a lot of different kinds of things. We ask about politics. We ask about living situations and networks of friends and social environment.

I think a huge advantage for some of the work I'm going to describe is that we aren't enriching for ascertaining on COVID status, because many of the other approaches while they're all useful in their own way, will tend to yield a population with more focus on COVID. They had it, friend had it, cousin had it. They're worried

about it. They have chronic symptoms. All very good reasons to participate in research. We hope that those people will participate in RECOVER.

On the other hand, if we're trying to get estimates of how common is this and what is it, we'd like to be as unbiased as we can in our sampling frame. So, this is a sampling frame that encompasses all adults 18 and older in the United States with some internet access. And that's an important caveat that we can come back to, the survey can be completed on people's phones, it's low literacy, it's fairly easy to do, but we do recognize we're not fully sampling everyone in the US. We use what's called a non-probabilistic enriched design. So, we oversample particularly hard to reach groups. We oversample small states where it's hard to get an adequate sample, because for the survey, we're aiming to get three to more than 400 people in every state, in every wave, generally with good success. And then we re-weight our estimates using standard survey methodologies to try to approximate the US population as a whole, either in a particular state or in the entire United States.

What we've worked hard to do is validate this work against other surveys that use more traditional methods, probabilistic designs, and to validate our results against administrative data. Data from RAND, data from the FBI, data other government sources, so that we can ensure that we're well calibrated. If we believe this number of people are firearm owners, that corresponds with administrative data. If we believe this number of people voted for a certain candidate, that corresponds well with registry data. And I listed one reference here in case people are interested in understanding that better.

Low cost, high yield, there are certainly more exhaustive and expensive ways to do this, but we were able to get it going early in the pandemic and have continued it since then, which is I think, a lot of its value over time. So, for example, because the survey includes depression screening scale, the PHQ-9, in every wave, we've been able to follow depression as it's waxed and waned in the United States over the last two years. So, for example, as of March, about a third of adults described moderate or greater depressive symptoms on the PHQ-9, a cutoff of 10 that we would often use for either referring for further evaluation or for treatment. So, that's the sort of thing, without getting into COVID, that we can do and have been able to do over time with survey data. It also lets us look state by state, which can be useful for certain kinds of questions.

Dr. Gallagher mentioned this, and I think it's really critical, it's really important to understand the environmental contributors to the biological phenotypes that we're seeing. So, it'd be a mistake to talk about depression in this country and even depression in the context of long COVID, without observing the massive impact for example, of economic effects early in the pandemic. So, this is from an earlier report that we issued, where we found that particular kinds of economic stressors, not surprisingly, were associated with greater levels of depression. So, for all our interest in understanding the biology of COVID, we can't ignore how important environmental effects are in depression in general, and in neuropsychiatric symptoms of COVID in particular.

Just as an aside, the survey design also lets us ask all sorts of other questions about COVID. This for example was an earlier paper where we found that depressive symptoms tracked with people's willingness to

endorse vaccine misinformation. So, people with greater levels of depression were more prone to absorb or endorse misinformation, probably reflecting a negative cognitive bias. So, all sorts of stuff we've been able to do with the survey. We're here today though, to talk about neuropsychiatric symptoms and long COVID more generally.

So, a number that is remarkably hard to generate and has been much debated, I will present to you on the basis of some recent data that's still in review. We wanted to know, how common is long COVID in the general population? So, we took the last eight waves of the survey between February of last year, July of this year. We asked of the people who told us they had a positive test at least two months ago, what proportion said they still had not recovered and still described symptoms. Very simple question, very face valid. If you had COVID at least two months ago, what proportion of people still have symptoms?

So, if you look across the entire United States in our sample, in this data from about the past year-plus, we found about 1.7% is the mean point prevalence of long COVID symptoms among US adults. Okay? If you limit that to people who tell us they had a prior positive COVID test, it's about 13.9%. So, conditional on past COVID, about 13.9% told us they had persistent COVID symptoms. If you take all adults or all 18 and older, walking around in the US at any given time, it's about 1.7% who describe long COVID symptoms. Those two numbers obscure a huge amount of sociodemographic variability. For example, the fact that the persistence of these symptoms seems to be much greater in people who identify as female. And I should point out, we don't have enough people who identify as non-binary or other, to say anything about, other than males and females in the survey so far.

Lots of variability by race, by ethnicity, by income, by education, by where people live. I think it just points out how much sociodemographic and environmental effects play a role, again, not just in depression, but in long COVID. One interesting point, there's a particularly complex relationship with age. So, while in general, it's been reported that older patients have greater risk or older people have a greater risk of persistence, what our data shows when we bin it, is that it's not linear and that actually those in the 50 to 59 age group probably have the greatest risk of persistence, followed by the 60 to 69-year-old age group. So, not necessarily a linear effect. And argues for collecting these large samples, whether with our survey approach or now what we are trying to do with RECOVER, to try to get into the weeds of who is at greatest risk.

Also interesting to note, when we ask people about individual symptoms, there's a lot of variability of symptoms by gender. So, for example, cognitive symptoms are substantially more common in women with prior COVID than men. 48% of the women with long COVID described having cognitive symptoms. Only 36.3% of the men with long COVID described cognitive symptoms. So, I think as we drill down towards neuropsychiatric symptoms, that's probably an important observation to pursue.

And if we want to understand post-COVID cognitive symptoms in particular, when we go back to our survey and we re-weight our samples, 0.7% of the adults in the US, roughly speaking, will report cognitive symptoms of long COVID. And that corresponds to about 6.1% of those who had a prior positive COVID-19 test. I'm

not saying these are the numbers. I'm saying with our method, which is different kinds of biases in a different sampling frame than electronic health records and COVID apps and other approaches, these are the numbers that we get. It's at least a useful starting point.

In the last couple of minutes, I want to switch gears a little bit, talk about mood symptoms, also data from our survey. This is work we published last year that reported, again using the PHQ-9, the prevalence of post-COVID depressive symptoms seems to peak around nine months after acute illness, but it's elevated beyond population baselines, which are the dotted line, really from during the acute illness throughout the subsequent up to 13 months. And probably need to update this because it's work from about a year ago.

So, more depression in people with prior COVID seems to peak, at least in this study, around nine months after. You can make some predictions about who's at greatest risk of post-COVID depression, if you want to get into these weeds, you are welcome to look at the paper. I think one important thing is we did find a strong association between self-reported severity of the acute episode and risk for subsequent depression. And importantly, these are not WHO categories, this is literally asking someone, "How severe was your acute episode?"

Two final points I want to make. You might say, "Well, rates of depression are high, is post-COVID depression the same as all-cause depression?" And two hints that that might not be the case. One is that the risk factors, the sociodemographic features that associate with post-COVID depression are somewhat different from those identified as being associated with depression in general. And this figure just makes that point that there are differences in effects of gender. There are differences in terms of where people live. There are differences in terms of income. Again, not saying this is biology, these may well be sociodemographic, purely environmental and economic effects, but big differences in what predisposes to risk for post-COVID depression versus all-cause.

And finally, one tantalizing, at least to me, finding, is that if you take everyone with depression in our survey and you say, "What are the symptoms driving that depression?" And again, this is work we published about a year ago. One of the really interesting things, everybody in this analysis is depressed, meets criteria for at least moderate depression. One of the things we see is that levels of motoric symptoms, either being slowed down or sped up and levels of suicidal thoughts are substantially, significantly greater among people with prior COVID compared to no prior COVID. And these differences in depression don't seem to be driven by things like sleep and energy that you might associate with having had COVID in the past.

So, I think the difference in symptomatology as well as the difference in risk factors tells me that while the two may well overlap, there probably is a post-COVID depression syndrome that likely overlaps with long COVID, but isn't necessarily the same thing. As far as mechanism, we and others are looking very hard at inflammatory effects in the brain. This is what I spend the rest of my time doing. I'm not going to have time to get into it today, but hopefully can come back another time and get into some of this work.

I just want to close by saying, the folks who've contributed to this work are really a large group of folks who've worked very hard during COVID to make sure that we have good information, good numbers, good

understanding of symptoms. And of course, I want to thank National Science Foundation who initially provided some funding for the survey and the NIMH who has funded a lot of my work with electronic health records in particular. Thank you very much. I'm happy to answer some questions.

Dr. Doug Bremner

My name's Doug Bremner. I'm from Emory University and I actually have COVID right now, so if I don't make sense, that's the reason, but at least I have some sympathy for what people have been going through. Next slide.

My disclosures are basically that some of the vagal nerve stimulation work I'm going to talk about, we get devices from ElectroCore. We have some subcontracts with other companies. I don't have any stock or financial interest. Next slide.

So, this is just the trajectory of COVID, has already been covered. About 57 million people identified in the National Health Service and an infection rate of 12%, 6% hospitalized. And those infected, the mortality was 2.2%. Higher mortality in earlier waves of COVID. Next slide.

And long COVID is, I guess we all know what PASC is at this point, it seems to be more common with severe infection, hospitalization and ICU course. Next slide. And some of the neurological complications. I just want to highlight that in addition to headache and fatigue, there's an increased risk of ischemic stroke, which appears to be related to the increased coagulation. Impairments in smell that seem to be related to the neurological changes. And you can get micro-bleeds in the brain and inflammation of blood vessels. Next slide.

So, what are the long-term effects of COVID? This is a recent study from Xie et al. that came out in British Medical Journal. 150,000 veterans who were infected with COVID compared to control groups and they showed about a 35% increase in anxiety disorders and 39% in depressive disorders. Those are hazard ratios, so 1.35 versus one risk for anxiety. They found increased use of antidepressants, increased cognitive complaints and sleep disorders. And people who were hospitalized with COVID were at greater risk of psychiatric disorders than those who were hospitalized for other causes. So this, in this study, did not appear to be a nonspecific effect of hospitalization. Next slide.

And this just shows you down there at the bottom, there's the hazard ratio. So, everything above one is a significant increase. So, you see increase in all anxiety disorders and depressive disorders, increase in PTSD, increase in use of antidepressants, also benzodiazepines and opioids. And additionally, there's an increase in substance use disorders following COVID infection. Next slide.

And overall, there's about 50% increase of any mental health diagnosis following COVID in this study. Next slide. And this is a survival curve showing the chance of survival without a psychiatric disorder. So, at the top there you see over time, there's a decrease in probability of being without a psychiatric disorder. So, at the follow-up period, about 80, 85% did not have a psychiatric disorder in the COVID group compared to about 90% in the

control group, and the similar for survival without being prescribed to mental health prescription medication or having any mental health diagnosis or medication. So, that's up to 360 days, that would be out to one year post-infection. Next slide.

So, there's been a lot of studies, as Roy pointed out, a lot of these studies are hospital record and chart review, often sample sizes of 60 or so, coming from different countries and it's difficult to make conclusions. However, overall, I think there is a pattern showing increased risk of psychiatric disorders is that it seems to be correlate with severity of illness. So, this is a meta-analysis from Schou et al. and Jennifer Frontera and Naomi Simon have a review that came out this year in JAMA finding essentially the same thing. This is a meta-analysis showing PTSD rates vary from seven to 43%. Increased risk of anxiety, depression. There's a question about OCD, there's least two studies showing increased risk of OCD and also psychosis, cognitive deficits and fatigue and sleep disorders. So, the conclusion was that there's an increase in these disorders with COVID infection. There's a tendency for symptoms to improve over time. So, the big question is, what's the long-term rate of these disorders? And of course, that's one of the questions that's going to be addressed in the RECOVER study. Next slide.

So, looking at, this is a study from Hall et al. looking at 1,958 adults reporting COVID infection, looking at cognitive function. They used a self-report of executive dysfunction and they validated decision-making tasks and trying to dose response increase in cognitive dysfunction, increase in self-reported symptom severity. And on this subjective task of decision task, there's a correlation with symptom severity. Next slide.

So, this just shows you with increased self-report symptom severity, going from asymptomatic to high and extreme symptoms, there's an increase in this Barkley Deficits in Executive Functioning Scale. It's a self-report measure of dysfunction. Next slide. And similar for this delayed discounting task, which was a natural task, you showed with increasing symptom severity there at the top with the very symptomatic, you get increases in both self-report executive dysfunction and in this task. Next slide.

This is another study, just showing that after hospitalization for COVID, this is in people with the most extreme, they had acute respiratory distress syndromes. Five months after release from hospital, they had a decrease on the selective reminding tests. It's just a test of declarative memory, ability to learn new words. And that was both for this long-term storage and then delayed recall task. Next slide.

So, what's going on that causes these neuropsychiatric effects? Well, we think that one of the consequences of COVID is it activates an inflammatory response, there's a release of interleukin 6, so-called cytokine storm, and that releases into the bloodstream, which can cause a neuronal injury and death. Next slide.

And this just shows you that the virus is absorbed in the air, it travels into the nose, upper respiratory tract, and attaches to the cell surface at the angiotensin converting enzyme, ACE2 receptor, and enters the cell, causes transcription of RNA, and then virus replication. That in turn causes an inflammatory response, and so you get a release of IL-6 or cytokine storm. There's macrophages and lymphocytes and monocytes that are attracted to these blood vessels, that they cause it endotheliitis. And that can cause micro bleeds in the brain and effects the

peripheral organs. Whether the virus actually enters the neuronal cell is unclear, but it is clear that it can cause neuronal damage. Next slide.

So, brain areas involved include the medial prefrontal cortex and anterior cingulate. So, this is of interest in that these are similar brain areas that are seen in psychiatric disorders, including PTSD and depression. The amygdala's involved in fear learning. The hippocampus is memory. And so, one idea would be that if similar brain areas are involved with long COVID, that could explain the increase in neuropsychiatric syndromes. Next slide.

So, this just shows you the medial prefrontal cortex that's involved in inhibition of fear responses and the amygdala and regulation of emotion. Next slide. And the hippocampus is that purple area and right at the head of the hippocampus is the amygdala. Lesions to the amygdala cause impairment and fear learning. And the hippocampus is involved in learning new lists and facts. There are some studies showing inhibition of nerve growth in the hippocampus with COVID, and a similar mechanism is seen in both PTSD, depression. Next slide.

So, what are the long-term effects? This is a study from Douaud, just a recent study in Nature of the UK Brain Bank. They were able to get MRI scans on 785 persons and through good luck, or if you want to think of it that way, got them before the infection with COVID, is part of another study, and then 400 tested positive for COVID and so they had before and after MRI scans compared to in both COVID infected and non-COVID infected. What they found is decrease in gray matter or thickness in orbitofrontal cortex and parahippocampal gyrus. Orbitofrontal cortex is adjacent to the olfactory cortex and probably plays a role in processing the smell information. And it saw greater changes in markers of tissue damage in areas related to the primary olfactory cortex and an overall reduction in global brain size. Next slide.

This shows you some of the areas involved. The orbitofrontal cortex and parahippocampal gyrus. The yellows areas are where there's greater reductions overall in the group of 400 COVID infected persons, both after infection compared to the baseline and compared to the controls. No changes in the controls. Next slide.

They also looked at the trail making task, it's a executive function task. And what they found is that with increasing age, especially after age 65, there was a greater impairment in the cases compared to the controls for both the trail A and trail B. This is just a task where you're asked to go from A to one, to B, to two, et cetera. Executive function cognition. Next slide.

This is from a study looking at white matter tracts and the blue areas are where there's significant differences in a group of controls compared to COVID infected persons. And what they found was a shift of water content in these white matter tracts. The blue is where there's significant differences in the patients compared to controls. Next slide.

This study was from Neisen, was correlating that the identification test scores, the ability to identify a smell. So, with decreasing ability to smell, there's a reduction in function in the orbitofrontal cortex and impairments in both the dorsolateral cortex and orbitofrontal cortex were correlated with duration of anosmia, which is the loss of smell. Next slide.

So, this is just showing that these red areas are pointing to areas of micro bleeds in the brain. So, there is evidence of probable disruption of the blood-brain barrier, increase in the C panel is the light pink, is the increase in infiltrates, inflammatory infiltrates. In the D panel, there's both macrophages. And in E, there's lymphocytes. And over here, it just shows the different areas. So, there's both anterior cingulate, cortex, midbrain, pons, and medulla. You get these infarcts and inflammation indicative of breakdown of the blood-brain barrier and injury. This is postmortem brain in people who died from COVID. Next slide.

This is showing areas of decreased metabolism with FDG PET. In the blue areas are a decrease in patients compared to controls, you see a reduction in orbitofrontal cortex, also in the insula there, and anterior cingulate and caudate. These are key areas involved in emotion. And there's some persistence up to six months in the olfactory/gyrus rectus, which is this blue area here, adjacent to the olfactory bulb, caudate and cerebellum. Next slide.

And this is showing decreased metabolism in patients with long COVID compared to controls is after several months, there's a decrease in orbitofrontal cortex, the olfactory gyrus area, also in the amygdala, hippocampus, and pons. The yellow areas are where there's greater decrease in a group of long COVID patients compared to controls. Next slide.

And this is in four patients here on the left, from pre to post-COVID, there's a reduction in size of the olfactory bulb. So, the COVID virus can actually attach to the olfactory tissue and cause possible damage to the olfactory bulb itself. Next slide.

And this is just to highlight that some of the brain areas that we've found in PTSD and depression include the hippocampus, also the prefrontal cortex, and this may be an approach to understanding the correlates of long COVID with neuropsychiatric symptoms. Next slide.

This is a decrease in medial prefrontal cortex function with traumatic reminders, areas implicated in long COVID as well. Next slide.

So, we have the COVID virus going into the nose here and attaching to these olfactory neurons, which it can cause impairment in this olfactory area. Binds to the ACE2 receptor and is taken into the cell. And so, one potential, that results in long-term inflammation in the blood vessels and increase in sympathetic function and decrease in parasympathetic function and peripheral effects on these organs, including the lungs, the heart, and I would add, digestion in the liver. And one intervention is neuromodulation. So, neuromodulation, which could include stimulation of the vagus nerve in the neck or the ear, or transcutaneous direct current stimulation, can reduce the IL-6 cytokine storm and sympathetic responses. And it also opens airways and enhances breathing, reduces pain and symptoms of PTSD and depression, and promotes neuroplasticity and modulates areas involved in long COVID. Next slide.

So, it has a number of effects on neurotransmitters involved in psychiatric symptoms, including acetylcholine, norepinephrine, and serotonin. And it both acts through the brain and to change these brain areas involved in emotion and it also has peripheral effects on the heart and inflammatory system. Next slide.

So, we've shown with stress in PTSD patients, there's an increase in IL-6, this is the key inflammatory cytokine that is activated by COVID. And we can block that. Here on the right, you see the blue is the sham IL-6, after the stress of a traumatic script, it's blocked by the active vagal nerve simulation. This just shows you how this electrical device is placed on the neck and it delivers an electrical current that stimulates the vagus nerve as it goes through the neck. Next slide.

And we've shown a reduction in heart rate, this is in patients with opioid withdrawal, so it has anti-sympathetic effects. Next slide. And this also shows a reduction in opioid craving, which we think is related to the sympathetic effects. Next slide.

So, this is the recent study from Badran et al., looking at transcutaneous auricular VNS, which is delivered in the year, in long COVID patients. And you see, this is baseline active versus sham control. You see this reduction in the active group, in the self-reported long COVID symptoms. And then that is the open label where you get a reduction in the previous sham group and then overall reduction. So, this is a small sample, but promising to reduce long COVID symptoms. Next slide.

And this is transcranial direct current stimulation. You see how this is electrodes put on the head and delivering electrical current. It's been used in psychiatric disorders with good effect. This is in patients in the intensive care unit with severe COVID and you see a reduction in number of days on the ventilator, in the active group compared to the sham, fake device group. So, these are the number of days that they're without being on a ventilator. They also showed a reduction in organ dysfunction and delirium at one month follow-up. Next slide.

So, in conclusion, long COVID mechanisms likely involve inflammation and involve brain areas involved in mood and emotion and memory, which overlap with the neuropsychiatric disorders, also involve brain areas involved with smell, including the orbitofrontal cortex and olfactory bulb, and one possible treatment opportunity might be neuromodulation. And thank you for your attention.

Dr. Simon: Well, I'm really grateful to our speakers today, who did a really amazing job wading through very challenging literature and presenting many of the challenges that are facing us in the field. Starting with Dr. Gallagher, who focused on how little we really do know about kids, although the data is emerging, but he really highlighted what I think each of our speakers spoke about, which are the enormous effects of the pandemic itself on the population and how hard it's been to differentiate that from other effects that might be going on as a result of infection, whether you can document the infection or not, and how population studies can answer some of these questions, but not all the questions.

I think he also nicely pointed out that it's always helpful to look back to other significant pandemics or types of infections and what we know about them, so we don't have to start from scratch. And I would say another

point, even though I'm not a child psychiatrist, keep in mind, to highlight from his work, that I think actually is relevant to adults as well, are the age related effects, especially in children, but we also see that in our older adult populations. It's something we hope to understand more.

Dr. Perlis then did a really scholarly explanation about some of the challenges to trying to understand prevalence, which seems like we should know this, if you step high level, by this point, we should know this, but wherever you look that you're going to have different biases to what we find, whether it be in what's documented in EHR, whatever kind of fancy methods. Even though it's wonderful to have natural language processing in addition to coding, because we know there's so many challenges in the coding, but even existing in the EHR, as I think some of our questions have pointed out, is the first left step and something that we have to face in all of our research as to what are our ascertainment biases that RECOVER, I think, is trying to address some of that, but it's obviously going to have some of these same challenges.

And then Dr. Perlis spoke about some ways to manage that in surveys, where you include broad swaths of the population to decrease your ascertainment bias, as well as some of the differences of considering time and how things might change over time. That I think we spoke only very minimally about today, in terms of the time course of when these things come on. And I'll just mention a couple things we can think about from RECOVER too.

And then we switched to Dr. Bremner who covered vast literature about the impact on the brain, despite his own illness. So, we're very grateful to you, to continuing to be with us today through all of this and to pull this through. And I think both of you have spoken about some of the really emerging, but unclear pathophysiologic mechanisms that may or may not include direct brain effects or secondary brain effects through a variety of mechanisms that could be associated with mental health.

And also, we're really fortunate that Dr Bremner gave us one example of how people are starting to think about what can we use about what we're learning, to possibly target symptoms. And I think that's another big question, we're not focusing on treatment in this particular seminar overall, could be an entire different seminar and we have a lot to learn about it, but this idea of, do we use what we know works for most usual presentations of the kinds of mental health conditions that emerge? Or, do we target something differently in the presence of long COVID? And I think the field needs to know way more about that to be able to have really good guidelines.

I was going to share just a little bit about what we're doing in RECOVER, but I think in the interest of time, I'm just going to pose some questions and I think most people know how to find the information on recover.org. Let me just share this really quickly, but also that there's multiple tiers that go on. So, we have some basic screening going on where people are getting initial screening, I'll just jump through it very quickly, and that passes them on to the next level. So, we have PTSD, anxiety, depression, we have some [inaudible 01:11:56] domains, social support, discrimination, some of what you've been hearing about that more in-depth, neurocognition and sleep measures. And actually, there's been an interest in trying to make sure everyone is assessed for suicidal thinking. That's a new change.

And then people can get referred to next levels, such as neurocognitive testing, MRI scans, and so forth. So, I'm just doing that really quickly in the interest of time. It's all posted on the website, but I think all of these speakers raise some questions that we can hopefully help to address through RECOVER, but also other ongoing studies that you're hearing about. These are the prevalence rates and predictors of persistence in PASC versus controls over time, knowing there's going to be some bleed between these groups, but looking across the country and then trying to do a deeper phenotyping when we do screen positive, so we can look a little more deeply in those patients.

And that includes things like the in-person neuropsychiatric interviewing that goes on, the mini diagnostic assessments, trying to separate the pandemic stressor effects from infection-related effects. And I have a spelling error here, sorry, typing this in as we're listening, but I just wanted to make the point that mood and anxiety disorders, which are amongst the most common things we've seen are stress responsive conditions. That doesn't mean it's only caused by environment. So, we want to be very careful that we don't say it's either this or it's either that. These things interact in the brain and are biological and biopsychosocial mechanisms that are likely interacting with each other.

We also barely touched on the variant effects and the phases of the pandemic, that we'll have some opportunity to look at, or the effects of preexisting psychiatric illness or medical illnesses, which could be also recurring in the setting of both pandemic and infection. You heard about social determinants of health, impacts of age, gender. Also, what people received, which Dr. Bremner started to raise, has barely been looked at and how that affects their course of illness.

And then the level of severity of initial illness, which seems to be not as strong as we initially thought, that many people are even emerging later with neuropsychiatric PASC symptoms, but we do want to look at that. What are the critical illness effects, other illness specific factors? What are the mechanisms, for example, in patients who are initially asymptomatic, how do they later go on to develop PASC and neuropsychiatric PASC? And what are some of the interactions with these symptoms over time? And as I mentioned, we'll be able to look at neurocognitive formal testing in a subset of the patients, as well as blood-based testing, MRI, sleep testing, and recorded information about prior history and naturalistic treatments.

So, I think in the last couple of minutes we have before Q&A, I would just pose to each of our discussants, what do you feel are the greatest lessons learned and the greatest opportunities for better understanding these dilemmas of what is going on and how can we understand the mechanisms or treatment of PASC? Let's start with Dr. Perlis.

Dr. Roy Perlis

So, I worry that one of the big gaps in our knowledge is the strain specificity or the variant specificity of some of these effects. So, I think in terms of what we've learned, I think we've learned a lot about the persistence

of symptoms and the nature of those symptoms. And as the last speaker pointed out, I think we're starting to get to mechanism. So, there's a convergence of some of the imaging work, some of the neuropsych work, some of the cellular modeling, although the cellular modeling so far is very, very early.

So, we're starting to get to mechanism, but I worry that again, we have this snapshot blurred over what are essentially very different viruses in some ways, at least in terms of their potential brain effects. So, I'm hopeful that we'll start to understand that, I think, as we have longer follow up from the arrow, when there are all of these newer variants to contend with.

Dr. Naomi Simon

There's a lot of complexity still to work through, but we're getting better and closer. So, I pose that same question to you, Dr. Bremner, in your review, what do you feel are the most interesting lessons learned so far and opportunities for the future?

Dr. Doug Bremner

Well, I think in my review, which I did to prepare for this talk, there was just the search for COVID in the brain, there's over 6,000 papers have been written in the past two years, that it's really remarkable, I've never seen anything like that in terms of the volume of what's been written. And probably a third of those are speculative "meta-analysis" case series review, "This is the perspective from XYZ country, with 60 patients."

And I find that there's a couple things I found really striking to another area, there's multiple parallels with another area that I've been involved in, in the past, which is the effect of an acne medication called Accutane, which is isotretinoin. One is that, there's a question of, does it cause depression and suicide? And you get a number of these studies where you have an N of 60, and it's, here's the view from this country or that country, I don't want to name a particular country, I don't want to insult anyone, but I don't think that kind of research really moves the bar forward.

And I appreciate Roy's perspective on the chart review, because a lot of these are chart review. And that was one of the questions that I came up with is, are these actually leading to answers that are biased and not providing better information? The other thing I didn't really touch on, another similarity with the isotretinoin is that there's one review paper about, it may be that the syndrome is very similar, so the PASC is very similar to the long-term effects of Accutane, and often there's overlaps with other things like chronic fatigue syndrome and some of these other chronic inflammatory conditions. And so, one of the threads is brain fog, a symptom that I think a lot of physicians may have ignored in the past, but it's something that patients complain about and we need to pay attention to.

So, looking at that other syndrome, you have brain fog, you have cognitive impairments, you have sexual dysfunction, right? That's another PASC symptom that has not been highlighted, but you see in some of these

other long-term syndromes. And so one paper was saying, well, maybe PASC is causing an increase in vascular damage in 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, they affect gene transcription, there are high levels of vitamin A, vitamin A is a retinoid, high levels of vitamin A can cause psychosis and neuropsychiatric symptoms. So, that's another possible mechanism. But I think the key area in my mind to hone in on, is the mechanism. So, is this an inflammatory response? Is there an actual invasion of the neurons by the virus? Is this a secondary effect of the inflammatory response causing damage to neurons in the brain? It's not a direct effect.

Dr. Naomi Simon

Yeah. Thank you. So, there's a lot to learn, I agree, is very interesting and inflammation is a very interesting story to try to understand more, especially as there is for people who are not as familiar with mental health, a lot of data understanding some kind of role in inflammation in many of these stress responses, but we could talk about this, I think for hours, but I know there's some questions and we need to wrap up this part. So, I'm going to pass along to our Q&A and thank our speakers again.

Lisa Newman

Thank you. Let's move on to Q&A. "How does mitochondrial dysfunction fit into the mental health continuum you all discussed today? And are you testing for mitochondrial dysfunction?"

Dr. Roy Perlis

So, I think the best answer there is we have no idea. We don't really understand mitochondrial dysfunction in psychiatric disease and only in a subset of neurologic diseases. Certainly, something people are looking at, those of us who do cellular modeling, certainly characterizing mitochondrial function as part of what we do. But anyone who says they understand whether and how mitochondria contribute to long COVID, I think is probably going beyond the data, at least the data that I've seen.

Lisa Newman

Okay. "Are you finding more women than men are presenting with long COVID memory issues? And are you finding more presenting with memory issues who had the ancestral COVID, Omicron COVID, or Delta COVID strains?"

Dr. Roy Perlis

So, I can answer that based on our survey. In fact, I think I showed in one of the tables, we do see substantially more cognitive symptoms among women compared to men. So, conditional on having long COVID or saying you have persistent symptoms, we do see more in women than in men. We don't have any understanding of why that might be. As far as variant-specific effects, I don't think we have enough data. We are certainly looking at it, we just don't have enough data yet to really weigh in on that.

Lisa Newman

More to come. Okay. "Given dysautonomia is a well-established comorbidity of post-acute sequela to infectious diseases, and that dysautonomia has direct physiologic impact on cognitive function and anxiety, have you all considered using self-administered NASA Lean Tests in your mental health studies, so, doing heart rate measurements, lying, sitting, standing to assess it as a physiologic underpinning to the ascertained mental health diagnoses?"

Dr. Doug Bremner

Well, that Badran studies, was someone that we collaborated with, Bashar Badran, in long COVID patients, they were doing auricular vagus nerve stimulation. They were also coupling that with what we call wearable sensing devices. So, they're teaching people how to put on these devices that measure various aspects of autonomic function. And then they're collecting the data in real-time as they're actually administering that treatment. So, the answer is, yes, we are moving towards ... Dysautonomia, it's probably the brain that causes the dysregulation of peripheral autonomic function.

Dr. Naomi Simon

And I just would point out that the neuropsychiatric committee of RECOVER has been reviewing the different SOPs and plans, and there is a focus on autonomic dysfunction, that is part of RECOVER.

Lisa Newman

"Are all the FDG scans before and after COVID, or can long COVID be identified by lower than typical values, lower than normal?"

Dr. Doug Bremner

Well, the long COVID studies are looking at, they're both looking at before baseline and compared to controls and looking at one month and six month, but some of them are looking at people with the diagnosis of long COVID syndrome, comparing them to normal databases. So, those brains that have the bright yellow areas showing where there's differences, those are significant differences from normal.

Lisa Newman

Okay. This is for Dr. Bremner. "Is neuromodulation similar or the same as neurofeedback therapy? There's an attendee who had a brain map that showed high theta waves and the storms growing through 30 months of the journey through COVID, and the person has seen some improvement with depression, with neurofeedback therapy."

Dr. Doug Bremner

Well, neurofeedback, which we've done studies in neurofeedback, it's a useful tool for a number of these conditions. The difference is that neurofeedback is sort of observing some physiological signal and then using the ... I'm not an expert on neurofeedback, but the basic difference is that rather than watching your physiological signal and modifying that through your own modification, with neuromodulation, you're actually delivering an electrical signal. So, that would be the difference. So, either delivering an electrical signal at the neck or the ear or through electrodes throughout the brain, something that hasn't been done yet would be using magnetic pulses, that's transcranial magnetic stimulation. So, these are all delivering some kind of external impulse.

Lisa Newman

Okay. And one of the attendees, an attendee and a COVID-19 clinical researcher, do you know if there's any longitudinal data on multiple COVID-19 infections on PASC neurological symptom prevalence?

Dr. Naomi Simon

I haven't seen anything. I don't know if either of you came across anything in literature that addressed that, having multiple different infections?

Dr. Roy Perlis

I haven't. I think it's really hard to study with a lot of the designs that have been applied so far. I mean, it's a critical question as we accumulate multiple infections, but for a lot of the reasons I mentioned with the HR stuff,

it's not trivial to capture that kind of exposure.

Dr. Naomi Simon

And even harder now with a lot of home testing and many people not doing...

Dr. Roy Perlis

Exactly.

Dr. Naomi Simon

But hopefully with some of the interviews and the three month follow-ups we'll, in the prospective sample, capture some of that in RECOVER.

Dr. Roy Perlis

Yeah. I mean, it's interesting, I think, hearing all these different perspectives about what we do know about long COVID makes a study like RECOVER that much more critical, right? Because it fills the gap between these other kinds of approaches.

Lisa Newman

All right. I want to be respectful of time today. This was a great set of presentations. Thank you to all of our panelists and thanks to the audience for joining us today. As mentioned in the chat and as I said earlier, an FAQ document, including a recording from this webinar will be posted on recovercovid.org, and it will include responses to all the questions, those asked in advance and those that were asked today. And questions about other scientific topics will be addressed in future webinars and again, answers to broader questions will be answered in the Q&A. So, Shane, if you will share the slide of upcoming webinars. Here's the list of upcoming webinars, so we look forward to having you attend. And thanks again to the panelists. We really appreciate it. Very informative presentations today.

Webinar Slides

To request a copy of the R3 Webinar slides, please email RECOVER_ACC@rti.org.

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/