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Approaches to investigating mental health disorders

Mental health is essential to a person's wellbeing, and mental health is a crucial component of the positive functioning and flourishing of families, communities and societies. At CNS Summit 2022, held 17–20 November 2022, Murali Doraiswamy asked Joshua Gordon from the National Institute of Mental Health to explain current limitations in the field of psychiatry and future steps to overcome these impediments.

Joshua Gordon is the director of the National Institute of Mental Health (NIMH), the lead US federal agency for research on mental disorders. He oversees an extensive research portfolio of basic and clinical research that seeks to transform the understanding and treatment of mental illnesses. As an MD and a PhD, he brings dual expertise as a clinician and neuroscientist to bear. Here, Murali Doraiswamy, professor of psychiatry at Duke University School of Medicine, asks him to explain the current and future aims of the NIMH in the field of psychiatry.

What are some of the most pressing issues our nation faces in the context of mental health?

Obviously, at the forefront of everyone's mind in the current era is COVID-19. There are substantial mental health effects consequent to the pandemic, whether we are talking about the general public or those unfortunate enough to have long COVID, which has myriad psychiatric manifestations. But we cannot forget that long before the COVID-19 pandemic, we were wrestling with a much longer-standing crisis in mental health care for our youth. Around 10% of children experience a serious emotional disorder. There is also tremendous unmet need in serious mental illness, with about 6% of people in the United States suffering from a serious, disabling mental illness, such as schizophrenia, bipolar disorder or major depressive disorder, at any given moment in time. These are tremendous burdens; each of these is among the top 20 health burdens in terms of disability, morbidity and mortality. Collectively, mental illnesses and substance-use disorders are the number three cause of disability in the United States. And of any single diagnosis, major depression is the number one cause of disability. Therefore, we are talking about serious disabling disorders. Then, if you come at it from, of course, my perspective as a researcher, as a scientist, and as someone who is overseeing the research portfolio for NIMH, the concerns here are threefold. Number one is getting a better understanding of the illnesses. Number two is getting better treatments. As you know, treatments do not work for at least a third of people with any one diagnosis. And number three, and this is one that many in this room will appreciate, but is not always the focus, is getting the treatments that we know work to the people who need them. It is estimated that about a third of people with a serious mental illness do not get any treatment, and something between a third and a half of those who do get treatment do not get evidence-based therapies. So, we need to do a better job in treating people, just as we need to get novel treatments for these tremendously disabling disorders.

Talking of treatments, NIMH has several exciting therapies in the pipeline (Table 1). Can you tell us about perhaps what is the most exciting one, in your opinion?

What is most exciting right now is not a single treatment but rather an approach to treatment: precision therapeutics. Consider one kind of high-tech treatment: deep brain stimulation, or DBS. DBS can be effective, at least modestly so, for depression in its current form. NIH is funding studies that are beginning to look for personalized signatures in patterns of brain activity and to target DBS to those personalized brain signatures. An example is studies by Edward Chang and Katherine Scangos and others at the University of California at San Francisco, in which they are detecting oscillatory signatures in people with mixed anxiety and depression and showing that if they can target those signatures with individualized patterned treatment, they can help people feel better. That trial is now moving forward with larger numbers. The idea that in an individual person, we can detect what is going on with them and precisely define the treatments that will help them is wonderful. We have similar programs that are using less-invasive therapies such as transcranial magnetic stimulation to target specific brain regions and patterns of activity within those brain regions. And on a wider scale, we and others are engaged in research to try to understand what biomarkers might help guide therapies that we know already work, such as drugs or psychotherapies, and get them to the right person earlier.

Talking of therapies, the hot buzz these days is around psychedelics. Is NIMH playing a role in supporting the research and development of psychedelics? Can you give us some examples?

The psychedelic field is actually quite active. I just came back from the Society for Neuroscience meeting, and the symposium on the basic science of psychedelics was standing-room only with a 15-minute wait out the door to get in to stand and listen to the scientists. It is a hot topic in psychopharmacology, and it seems very promising. The early returns from small studies suggested the possibility that these drugs could be truly transformational. Unfortunately, as with most things in psychopharmacology, when you do the larger studies, the efficacy is lower than you might have hoped for. But nonetheless, these drugs look as if they are going to be effective therapeutics. We have not historically supported those clinical trials and, frankly, we do not see a big role for NIMH in supporting clinical trials in psychedelic research when there are hundreds of millions of dollars of private money going into this. But I think there are some areas in which we need to get answers that the private sector is not as interested in answering. For example, can we target psychedelic drugs or change psychedelic drugs so that we can affect specific receptor pathways

Table 1 | NIMH-supported major research initiatives

Ongoing initiatives	
Accelerating Medicines Partnership Program – Schizophrenia (AMP SCZ)	A public–private partnership to improve success in developing early-stage interventions for patients who are at risk of developing schizophrenia.
Adolescent Brain Cognitive Development Study (ABCD Study)	A landmark study that explores the environmental, social, genetic and biological factors that shape a person's future.
Advanced Laboratories for Accelerating the Reach and Impact of Treatments for Youth and Adults with Mental Illness (ALACRITY)	An initiative that fosters innovative research ideas and transdisciplinary collaborations to transform the care of severe psychiatric disorders.
The Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) Initiative	An initiative that is laying the foundation for developing novel treatments and interventions for mental illnesses.
Early Psychosis Intervention Network (EPINET)	A network that includes regional hubs and more than 100 clinics across the country that provide coordinated specialty care, a multi-component treatment for early psychosis.
Helping to End Addiction Long-term Initiative (NIH HEAL Initiative)	An ambitious, high-priority effort to speed scientific solutions to stem the opioid public health crisis.
Practice-Based Suicide Prevention Research Centers	Integrated, transdisciplinary programs aimed at developing and testing effective approaches for reducing suicide rates in the United States.
Selected complete initiatives	
Fast-Fail Trials (FAST)	An initiative that aimed at providing a quick way to test new or repurposed compounds for their potential as psychiatric medications.
Human Connectome Project (HCP)	A project that aimed at mapping the macroscale connections of the human brain, which led to new data models, informatics and analytic tools that advanced researchers' ability to image and analyze brain connections.
Rapidly-Acting Treatments for Treatment-Resistant Depression (RAPID)	An initiative in which researchers identified and tested promising pharmacological and non-pharmacological treatments to rapidly help people with treatment-resistant depression.
Recovery After an Initial Schizophrenia Episode (RAISE)	An initiative whose research findings helped expand coordinated specialty care treatment programs across the United States, which helped lead to the formation of the Early Psychosis Intervention Network (EPINET).

Source: NIMH

downstream of the serotoninergic 2 A receptors, to understand whether you can dissect the roles of efficacy versus psychomimetic qualities, and to see if we can improve upon the existing drugs and reduce their potential for abuse or side effects? The necessity for guided psychotherapy, which is something that some of the studies,, but not all of them, are looking at is something that we need to resolve from a public health perspective to make sure that these therapies can reach the maximum number of people that we would like them to reach. Thinking in the future towards the next generation of therapies, which we are always doing at NIMH, we would like to know the mechanisms by which these drugs work in the brain. We have been collaborating with the National Academy of Medicine and with numerous other groups to come up with a sort of research plan in psychedelics. NIMH priorities in this area have been published (https://grants.nih.gov/grants/guide/notice-files/NOT-MH-23-125.html), so I encourage scientists to look at our notice and consider submitting applications for research in these important areas.

Another area that is topical right now is the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative, which is coordinated across ten institutes and centers at the US National Institutes of Health (NIH), including NIMH. It is approaching its halfway point. What makes this effort different and unique from other large-scale efforts, and what are some recent findings? Can you share some insights?

This effort has been going on in the planning stages for about 8 years (Table 1) and in the funding stages for about 6 years now. First, one of the things that makes it unique is that it has captured the imagination of policymakers and politicians to the point at which the US Congress has set aside a dedicated funding stream for it, and a substantial one. The current funding is around US $600–700 million a year, depending upon the year. The second thing that makes it unique is that it is a big scientific effort combined with technology and innovation. In the early stages, we funded many groups all around the country and really challenged them with thinking outside the box, bringing in additional researchers, not just neuroscientists, but engineers, physicists and behavioral scientists, to design technologies that break open the brain in new ways. And they responded tremendously. We have electrodes – whereas we used to be able to record from a few tens of sites in the brain at one time, now we can record from thousands of sites in the brain at the same time – and optical imaging techniques that can go through the skull and image neural activity on the surface of the brain in laboratory animals and even in humans. Therefore, we can image the entire surface of the mouse brain at once, or a whole chunk of primate brain or human brain at once, monitoring the activity of large numbers of neurons. We also have another technology that is able to get at the genetic information, RNA and DNA, of a single cell and then do that millions of times over. That is the early phase, and in the second phase, it has really switched to the big science efforts.

What are we doing with those technologies? Well, in the case of single-cell technology, we are creating an atlas of all the cell types in the mouse brain. We have begun piloting that for primate and human brain as well. This is going to create interactive web-based libraries that are going to be precious tools for scientists. Anytime scientists discover some new phenomenon, such as studying the hippocampus and the prefrontal cortex, they will be able to go into these areas and figure out the different cell types, as well as tools that they can use to manipulate those cell types, turn them on, turn them off, monitor them, and learn everything that they need to know about the brain areas of interest.

Importantly, that toolset will be designed so that we can manipulate those cell types in

the human brain as well. Therefore, we are not talking about DBS of whole areas or tracts anymore, but of precise brain circuits. I think that is the technology that 10 years ago we thought of as science fiction, and now we are literally building out those technologies. I should mention that these are efforts that require scientists to give up their egos and work for years on clinical trials to bring together lots of people, since we need lots of folks to be able to carry out a large clinical trial. We are doing the same thing when we are talking about building an atlas of the mouse brain, for which we have hundreds of scientists distributed across tens of institutions around the United States and, indeed, around the globe, all working together with the same protocols, with the same machinery, with the same technologies to get multimodal information about every single cell in the mouse brain. And as I said, we are moving in that direction for primates and humans as well.

It is, therefore, very exciting from the perspective of the technology, from the knowledge that we are gaining, and also from the idea of the scientific process. We want to take that process piece and bring that to research and mental illness so that we can do large single-cell studies of post-mortem tissue from people with brain disorders and break those open with the same level of collaboration and thoroughness that the BRAIN Initiative has done in the basic science arena.

And all those data will be in the public domain eventually, I assume, right?

Yes. This is the mantra at the NIH. It has been that way for a while. Both people who participate in and researchers who conduct NIH-funded clinical trials know that at the conclusion of the trial, the de-identified data should be put in the public domain. US President Biden's Memorandum of August, 2022 (https://www.whitehouse.gov/ostp/news-updates/2022/08/25/ostp-issues-guidance-to-make-federally-funded-research-freely-available-without-delay/) requires that within a few years, every piece of data that any NIH-funded scientist has generated from those grants should be put into the public domain and shared. We at NIMH have been at the forefront of that. My predecessor created a database to store all our clinical trial information. We made the decision 2 years ago to require all our clinical trials to put their data in our database, so it is all there in the public domain at the conclusion of a trial and or after the publication of the data or after the conclusion of the grant. We are moving most of our big datasets to even pre-publication release of data, such as the Adolescent Brain and Cognitive Development Study (ABCD Study), that is all released before publication.

We are pushing that as much as we can in many of our large collaborative studies, including a study called AURORA, which is a longitudinal, multi-modal study (clinical, imaging, digital and genomic assessments) of post-traumatic stress disorder.

What is the role of public–private partnerships, and how can life-science companies work with NIMH in these kinds of partnerships? And can you give some examples?

Let me start with this example. The Foundation for the National Institutes of Health (FNIH) is our partner in most private–public partnerships. This is a foundation that is set up with the approval of Congress to facilitate these interactions. It has several different programs, including a biomarkers consortium, in which we participate. Through that consortium, we are working on US Food and Drug Administration (FDA) approval for neurophysiological and behavioral biomarkers in autism, for example. Another example is the Accelerating Medicines Partnership (AMP) program, a framework for public–private partnerships in drug development. Three years ago, we set up the first AMP in psychiatric disease research: AMP Schizophrenia (Table 1). This is a collaborative effort of several pharmaceutical companies, patient advocacy groups and nonprofits, along with the NIMH, FNIH and FDA. This project has set up networks of community-based clinics to recruit and study people at risk for schizophrenia. We hope to embark on proof-of-concept clinical trials that are aimed at helping those people with the symptoms that they are dealing with now, as well as potentially reducing the conversion of psychosis.

The way this works is that the FNIH acts as our intermediary. They work with the pharmaceutical companies that are interested to set up the rules of the collaboration. We have a governing board, and all the data that are gathered are in the pre-competitive space, and 6 months after acquisition, they are released to the public. But for 6 months, the partnership has the data to peruse beforehand. And we think this is an outstanding model. We want to develop databases that we can use to develop and apply biological and behavioral biomarkers. Couple that with all the kinds of work in the space of wearables and, of course, in electronic health records or clinical trials. We want to develop the capacity to interrogate those databases to do a better job at treating disorders, or predicting who is going to respond to which treatments, and/or who is going to have which longitudinal course. The idea is to build upon clinical diagnostics to see how much better we can do. Those are the kinds of partnerships we are looking forward to.

So if someone is interested in actually either joining one of the existing partnerships, or wants to approach you or someone about starting a new one, how should they start? Do they approach you or the FNIH?

You can approach me, and I can refer you to the right people at the FNIH. We are looking to build partnerships right now with the FNIH. The new chief executive officer of FNIH, Julie Gerberding, is really interested in mental health and has made a commitment to expanding FNIH's role in collaborating with us and the other institutes, such as the National Institute on Drug Abuse and National Institute on Alcohol Abuse and Alcoholism, that are in the mental health space.

Another area that emerged over the past 2 years of the pandemic is digital health and digital mental health. What are your general thoughts? Because at least six or seven so-called digital therapeutics (cleared by the FDA for specific mental disorders such as substance abuse or chronic insomnia) are on the US market, and there are thousands of other consumer wellbeing apps. Also, does the NIMH have an active research portfolio in this area?

I think digital mental health has already been tremendously valuable. It will continue to be tremendously valuable from my perspective. Again, as a scientist, what I would really like to see is more digital health apps and companies going down the road of getting FDA approval, of proving that they work for a mental illness. I am all for mental wellness. I absolutely want to maintain wellness. But remember that 6% of adults and 10% of kids have a serious mental illness or serious emotional disturbance, a diagnosable condition that needs evidence-based therapies. If the digital health community does not respond to that tremendous need by proving that their products work for people with the most severe forms of mental illness, then they are not doing their service to reduce that disability. In general, there is a lot of great stuff out there, but we

need more of it to be proven to work for the most severe cases.

Accordingly, that is what NIMH is funding in this space. We are funding both academic scientists and companies to do that work to develop novel approaches and to test them in illnesses with traditional outcome measures, as well as other outcome measures that might be better.

I think we also need to develop standards and platforms. I know that as a practicing psychiatrist, I am not going to learn seven different platforms for seven different digital apps that I might need to treat even three patients, because they all come in with multiple problems that are going to benefit from multiple solutions. I need platforms that I can use where different developers with evidence-based therapies can put their products onto a platform that I can use in my practice to treat everyone or a lot of people, and patients can also use to solve multiple problems. That is another thing that we would like to see in this space.

Are there large multicenter digital therapeutic trials that NIMH is funding?

We do not generally fund large multicenter trials. We leave that up to private industry. If private industry does not answer that call, we may have to, especially because of digital therapeutics. One thing that we do fund that supports this space is the Mental Health Research Network. This is a collaboration between scientists and a number of healthcare systems, including Kaiser and some other health maintenance organizations. They are able to do very large clinical trials on the cheap, because they deliver it all through their electronic health record systems. We cannot afford the traditional, very expensive clinical trials, but we can afford to do trials that cost a couple of bucks per person in terms of that space.

How can digital health companies work with the NIMH? And are they already examples of such collaboration?

They absolutely are. The easiest way is if you qualify as a small business with the federal government, then we give small business grants. Even companies that are well funded will apply for these small business grants because it gives them, of course, the imprimatur of being an NIH-funded investigator. That gives us the opportunity to also impart our priorities. Again, if you are going to have an app, make sure it works for a diagnosable mental health condition. Then the app can be put on a pathway to getting approval as a medical device. This one avenue, and then a second avenue would be, again, thinking about whether we could work with the FNIH to create some sort of precompetitive atmosphere in which FNIH would be interested in fostering a public–private partnership.

One of the problems that I can see readily that would fit this model is that with many of the digital therapeutic apps, even ones that have been cleared by the FDA, the engagement drops off over time, and the attrition rate increases to where, after maybe 6 months, 50%, 60% or 70% of people have dropped off these apps. Thus, we may not have long-term efficacy. And we know that conditions such as depression and post-traumatic stress disorder may need lifelong treatment. Therefore, is that an example of a pre-competitive space in which, potentially, we can focus on increasing patient engagement and reducing attrition? How do we even define attrition? Because it is defined differently – even engagement is defined differently – in some of these gamified apps.

That is a great point, Murali. And I will just point out a couple of things about that. Number one, NIMH is beginning to address the issue of engagement with some of the biomarker studies we are trying to do. We are trying to build engaging approaches. Some of our studies that do longitudinal work, such as the ABCD (Adolescent Brain Cognitive Development) study, have really solved the problem of engagement, at least in research studies. Therefore, trying to figure out how to do that in ongoing clinical care will be compelling and interesting, as well as having the potential for collaborative, pre-competitive work. There is another area of engagement in medicine, behavioral medicine, that the NIMH has been working in for a long time and has had reasonable success: adherence to medication for people living with human immunodeficiency virus (HIV). We have a whole AIDS research division that has studied adherence to medication in HIV, pre-exposure prophylaxis, etc. across a wide range of contexts. And there are proven principles that do a modestly effective job of ensuring adherence, although I would not say that the problem is completely solved. We have the expertise, at least in terms of designing research studies around adherence in general, that I think could be applied to the digital space to look for solutions to increase engagement over the long term.

Related to digital health, the other buzzwords are AI, big data, real-world data. Any thoughts? I know you are very interested in getting real-world data, especially merging electronic health records with other kinds of biomarker data.

We have to think about what our niche is at NIMH in this regard. We are fundamentally a mechanism-focused biomedical research organization. We want to expose the targets that private partners can use to develop treatments, whether they are drug treatments, digital treatments or psychosocial treatments. That is our job: to expose mechanism. So that is what we think about when we think about big data or artificial intelligence (AI)-driven approaches or really any computational approach. In this space, yes, we are doing things such as using AI on big datasets with neuroimaging to see if that can do better predictive modeling for patients, to decide whether a patient is going to respond to treatment A versus treatment B. That is an important approach that we want to try to help foster, even as many private companies do in their own research. But our focus is on trying to build off our theoretical understanding of how the brain works to build the better datasets of the future that are going to do a better job than what we can do today.

An example of this approach is an initiative called IMPACT that we are just launching now. We just got approval from our council to do this in September (https://www.nimh.nih.gov/funding/grant-writing-and-application-process/concept-clearances/2022/individually-measured-phenotypes-to-advance-computational-translation-impact). IMPACT is an effort to define theory-driven behavioral tests that get at the computations the brain needs to solve. How do I determine what thing in the environment I need to learn about? How do I stop a pre-potent action that I learn now is wrong? These are well-defined, computationally formally described behaviors that we can map onto specific circuits of the brain. We want to build out tasks for these functions that we can roll out to people in existing longitudinal cohorts, such as the NIH All of Us cohort or disease-specific cohorts that we hope to build in schizophrenia, bipolar disorder, depression and other conditions, so that we can see whether we can carve disease better at its joints by using these theory-driven tasks. This is going to create datasets that one then can mine to ask the following question: can we determine who with bipolar disorder is going to respond to lithium

versus carbamazepine? Or who with depression is going to benefit best from transcranial magnetic stimulation, or from fluoxetine, or from a psychosocial intervention? Or, even more to the point, can we carve up bipolar disorder into the part of it that is better linked to mood disorders, and the other part of it that is better linked to schizophrenia? To do that, we know we need to fold in genetics and multimodal data. We need a better understanding of how things go wrong in the brain on a large scale. And so that is what we are interested in doing. We can start with the mechanism, build the data sets, and then mine them, so that we have a better understanding of what we are studying.

I understand NIMH has recently announced a new approach to mental health disparities research, which is such a hugely important area. What is NIMH doing to mitigate these disparities in the course and outcome of mental illness, both clinically and in the research setting?

First, in everything I have discussed above, we are more and more rigidly enforcing the need to recruit a diverse set of participants. That is why we want to work with the All of Us cohort, which includes participants from different races, ethnicities, age groups, and regions of the country. They are also diverse in gender identity, sexual orientation, socioeconomic status, education, disability, and health status. Second, we need targeted studies in communities that have been traditionally under-represented in our research endeavors. And we need not only those studies, but also to develop the relationships that will allow those studies. We want to focus more on community engagement, building the capacity to conduct research in these communities, and building the alliances that allow that research to be conducted. We have funded a wonderful early-stage investigator, Sidney Hankerson, in New York, who is working on engaging with churches to build relationships for mental health research in the communities in northern Manhattan. This is one example of the kind of thing we know we need to support more of. We have therefore created a whole new office that is focused on disparities research to really try to build that program within our portfolio.

Joshua A. Gordon was interviewed by P. Murali Doraiswamy

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Competing interests

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