

Ken Duckworth:

Hello, everybody. I'm Ken Duckworth. It's my good fortune to be NAMI's Chief Medical Officer. This is part two of Ask the Expert series on cognition. Cognition being one of the keys to the constructs of recovery, relationships, keeping a job. Last month, Susan McGurk and Kim Mueser from the Boston University School of Psychiatric Psychosocial Rehabilitation, discussed their program called Thinking Skills for Work. So this is the second half of that and I'll tell you a little bit about that in a moment. Next slide, Hagen.

We have a helpline staffed by over 150 volunteers with lived experience. It's a support line, it's not a suicide prevention lifeline, but if you're looking for resources, places to go, or if you're just plain lost in our fragmented, chaotic mental health system, we love our helpline and we hope you take advantage of it. Next slide, please.

People ask questions in the chat, which we love and I'll get to them, but I want you to know we have more than 60 ask the experts in our portfolio, so it's like a library. So if you're interested in how to help somebody who can't see that they're sick, we had Dr. Xavier Amador, if you're interested in postpartum depression, we had Dr. Marlene Freeman, if you're interested in bipolar disorder and what's happening there, and so on. So what I want you to know is the questions that you ask may not be just on cognition. Many of them can be answered in this series, which is all available on our website. Next slide, please.

Okay, so Dr. Matcheri Keshavan is a friend of the family of NAMI. He has trained on three continents, trained in India, then Vienna, then at Wayne State in Detroit. Then he comes to Harvard where he is a full professor and the academic head of psychiatry at the Massachusetts Mental Health Center and the Beth Israel Deaconess Medical Center. Kesh, as he is known affectionately to many of us, is the NAMI Scientific Award winner from a few years back for his work on early psychosis, cognition, and a compassionate approach to people who live with schizophrenia. He's written a lot of articles, a lot of books, he's a big deal. He also appears in NAMI's first book, doing a nice write-up about the early intervention program for psychosis called, Coordinated Specialty Care.

We asked Kesh to do a summary of the brain science aspect of cognition and I think you're going to enjoy his talk. Kesh, thank you for everything and for today's talk and I'll be back at the Q&A component.

Dr. Matcheri Keshavan:

Okay, thank you very much, Dr. Duckworth, and it's an incredible honor for me to present to this group, which I have done before many years ago, as well as when as Dr. Duckworth mentioned, during the National NAMI Convention, where I was really incredibly honored to receive one of the awards.

So today, I am going to speak on, as Dr. Duckworth said, the second part of cognition and schizophrenia. Dr. Kim Mueser and Susan McGurk with whom I work closely in Boston, they have a somewhat different approach to cognitive remediation. The approaches are similar, but the focus is different. So I'm going to give more of a brain focus to this presentation. I hope you're all able to see this slide, which I will now put into slideshow mode. Can people still see this? Great. So this is where I do my work, Harvard Medical School at the top left, and my main collaborators are in the University of Pittsburgh on the right side, and Mass Mental where I'm sitting right now, is in the middle.

And so the key points I'm going to make today are a little about schizophrenia. The nature of this illness, it's a disease of the synapses, and the core aspect of this illness is the cognitive impairment. That's the part one of what I'm going to talk about. The second part is I'm going to talk about a property of the brain called neuroplasticity, which is a fundamental principle behind any approach to cognitive remediation or cognitive enhancement as we might call it. The third part of what I'm going to talk about is cognitive remediation, the particular approach that we use is called cognitive enhancement therapy. It's an effective approach, it's a durable approach and it's a recovery focused approach. I'm going to tell you about how it is done and also about the data that we have showing its effectiveness in three independent, randomized controlled trials.

And finally, I'm going to give you some future directions as to understanding cognition and also improving cognition in people with not only schizophrenia but other forms of serious mental illness, including early intervention, exercise, improving sleep, using brain stimulation, and using digital devices like smartphones, using biomarkers for selection of who might be the best candidates, and also how cognitive remediation can be implemented in the community. So those would be the next steps, directions that I'll be speaking about.

First about schizophrenia itself. You all know that schizophrenia is not... It's a syndrome, there are multiple symptom domains. You all know that at any given point in time, about a half of people with this illness have psychosis, characterized by hallucinations, delusions, and thought disorder. And about a half have mood symptoms as well, depression, anxiety, stress-related relapses, and so on. And about two-thirds have negative symptoms, which include lack of motivation, lack of ability to experience pleasure, lack of energy, social withdrawal, and lack of... Much too thinking and impoverishment of thinking and so on. But the most common set of symptoms, which is present in over nearly 90% of the individuals with this illness is cognitive impairment. And it is the cognitive impairments that lead to the disability in this illness. Why is it that the majority of people with schizophrenia are unable to have full-time employment and are functionally disabled? It's because of cognitive difficulties, not because of psychosis. And the negative symptoms are another important cause for functional difficulties.

So, an important and unmet need for schizophrenia is on how to improve cognition. Medications that we now have, what we call anti-psychotics, are effective in improving psychosis and there are medicines for effective symptoms, but there are no medications so far on improving cognition, even though there may be some ideas in the field and some new medicines, which I can talk about at the question-answer session or later.

Now, a little bit about schizophrenia itself. What causes this illness? The current thinking is that schizophrenia may be related to losing too many synapses. Perhaps related to genetic factors, perhaps related to some environmental factors interacting with each other. What you see in the top right is an animation of the brain as scanned consecutively over several years, and what you see is a progressive thinning of the cerebral cortex during the period of adolescence. And the more blue it is, the more thinned out the cortex is. That's a normal thing. You can see this white line during the period of adolescence. It's beginning to reduce the amount of gray matter that exists there up to a certain point. To make the brain more efficient, that's how evolution has determined our brain's development. To be more efficient, you have to be a little bit more lean and trim.

But if that goes a little bit haywire and if due to a disease process there is an excessive or are a rapid decline in synapses, which happens during adolescence, perhaps due to some genetic reasons, maybe even immunological reasons. And I won't have time to go too much into the details of that, but I can tell you that there are some really exciting developments in the field about why this might be happening in some individuals who are at risk for psychosis. So that may lead to a situation where there are fewer synapses than you need. So at the top, you see the abundant synapses growing all the neurons that are characteristic of a healthy individual, but the bottom two neurons you see here, those synapses have been kind of diminished or lost. And that might lead to this cognitive impairment as you see at the bottom. And I'll come back to that a little bit later again.

So the next part, let me take you through, what exactly are the cognitive deficits in schizophrenia? There are two kinds of cognitive difficulties. The first is like the surgeon who comes onto the operation theater and doesn't know what exactly he's trying to do. Which organ does he have to cut? So that requires straight-up memory, that is called neurocognition. And then at the bottom right, you have this cartoon where the individual is trying to propose but is not reading the face and figuring out the emotion on the other person before doing so. That requires a certain kind of cognition, which we call social cognition. So neurocognition involves speed of thinking, memory, attention, reasoning, and what we call tact or social cognition, and also the ability to think strategically. So you have a little mnemonic built in there.

So, cognitive impairment begins early in the illness, maybe even present before the illness, during the pre-morbid phase of illness, and gets a little bit worse during the prodromal phase of illness before any psychosis has developed, but there are subtle changes in personality that are beginning to happen and subtle, mild or what we call attenuated positive symptoms or attenuated negative symptoms are happening. And then there is the more established first psychotic episode and then the more chronic illness. And what happens is cognition declines, beginning even before any symptoms develop, and also during the early mild symptoms which we call the prodrome. And well established by the time of the first episode and then maybe a little bit worse after that. Thankfully, cognitive impairments as far as we currently know, do not decline too much after the first psychotic episode. There may be a little bit, we'll talk about that a bit later again.

So now, one thing that has been found in repeated studies is that as I said earlier, the majority of the functional disability in schizophrenia is a result of cognitive impairments. This slide on the right side of this slide shows the effect size of how much cognitive impairments contribute to impairment in day-to-day functioning. Just think of a simple example. Let's say the person wants to go do some grocery shopping. You have to plan, and you have to decide what you want to get, and you have to remember, maybe put it down on a piece of paper. And then go to the grocery store and read it and pay attention to what exists on the shelves, and then decide to implement and actually purchase and make those decisions. Every one of it, of this task is a separate cognitive function. There is memory, attention, executive functions, and decision-making. All of those attributes are critically important to our day-to-day life. So there is no surprise that impairment in cognition leads to impairment in day-to-day functioning.

I'll take you through the five key elements of cognitive impairment in psychiatric disorders, in particular, schizophrenia. One is what is called speed. It's like your computer speed and the faster it is the better. So a simple test of that is what we call the trail-making test. You ask the person on a piece of paper, take a pencil and go as quickly as possible from one number to the next number to the next number to the next number to the next number and so on, as quickly as possible. This is the simpler version of what we call the trail making test. And a little bit more complicated version of that is what is called trail making B. In that, the person has to move from one number to the first letter to the next number to the next letter and so forth. So there's a little bit of complexity, cognitive complexity built into this. So not only is speed of thinking involved and attention, but also some immediate memory as to what did you do just before the next move and so on.

And that is taken even a little bit further by a test here which you will see here, which tests a particular aspect of our mind, what is called working memory. So the person is in front of a computer and there are a series of numbers that are appearing and has to wait until a point where the same number appears two numbers later, and then only press the button. So the number seven came two numbers after the previous number seven, so you press that. So this requires the ability to keep in mind what was the previous letter and the letter before that and so forth. And this can be made more difficult by adding more number of letters or how many numbers ago was the same number presented, and so on. So which is why it is called N-back task. This requires a particular kind of memory, what is called working memory.

You can think of working memory as a mental scratch pad. When we go through our life and we are trying to do various things, we put things onto our scratch pad in our brain, called the dorsolateral prefrontal cortex. So when a person is actually trying to remember things like this, just like when you're trying to make a telephone call, you look up the book and you would hold it on the top of your brain for a fraction of a second or a few seconds and then dial the telephone. And that is called the working memory and consistently when a person performs this in a brain scanner, it lights up a particular part of the brain called the dorsolateral prefrontal cortex. It's like a working memory muscle in the brain. So, keep that in mind as we go forward. And of course, it can be simple like the person only presses zero whenever it appears without a memory, and that is a test of attention. And even attention involves the same parts of the brain, like the frontal and the parietal cortex.

Now I'll show you a little bit more interesting kind of test that exercises another different muscle in the brain. So those of you who can speak loudly and maybe you can speak to yourself, name the color of the word that appears. Here you got blue, yellow, red, green, blue. So my brain suddenly stops. The word blue is printed in yellow, so the brain has just got confused. That's because the brain can only focus on one thing at a time. And this phenomenon, when the brain slows down and you pick up an error in what you're trying to do, that requires an error monitoring part of the brain. It's called the oops effect. Your brain says, "Oops," remember it has the STROOP effect. That's the kind of test psychologists use. And which muscle in the brain does it use? It uses the muscle in the inner part of the brain called the anterior cingulate. That's the muscle in your brain that catches your own mistakes and corrects yourself. So we need all of these different kinds of muscles.

Another kind of muscle in the brain involves problem solving. So here is a somewhat more complicated test, where the person has to classify a set of cards on the table based on some property. Maybe it is just on the number of the objects or the shape of the objects or the color of the objects, and so forth. And the person will not know what is the principle behind which this classification is happening. He has to figure that out based on the psychologist saying, "You are correct or you're not correct," and so on. And then in the middle of the test, the rules change and the person has to figure out what the rules are and so on. This is a test called the Wisconsin Card Sort, requires some problem solving ability. Again, that requires the prefrontal muscle, dorsolateral prefrontal cortex. Think of it as the side of the brain when you think of something you put hand on the front of the brain, frontal side of the brain, that is where the thinking or the thinking muscle exists.

Now, there is another part of the muscle which is the emotion recognition muscle. So here the person is asked to look at a pair of eyes and say what is the emotion behind this pair of eyes? Is it anxious? Is it angry? Is it happy? And so on. And in another task, the person is just asked to say whether it's a male or a female pair of eyes. And then the brain scan picks up all the parts of the brain that are related to emotion recognition. And there is a particular part of the brain, the circuit, which recognizes emotions, which involves some parts of the frontal lobe and some parts of the side of the brain, the temporal lobe, and an inside part of the brain which you don't see here, called the amygdala. So that is the emotion circuit. And so here is my cartoon of the brain having different muscles. We have actually a study going on called the BICEPS Study, which actually examines this kind of brain circuitries in different kinds of emotional states.

Now, another aspect of mental cognition processes is in this set of slides. If you haven't seen this before and if I were to be able to ask you a question, I might ask you what this is. Most of you will not be able to say what this is. Almost 100% will not be able to unless you have seen it before. But some of you will be able to say what this is at this point, or the majority will be able to say it. The majority of people, healthy individuals will be able to say that this is a watch at this point. And even a larger number will say it is a watch at this point, and of course you know what it is.

But people with serious psychiatric disorders like schizophrenia have the difficulty in detecting a pattern which requires filling up the blanks in our brain. If there is a fragmented picture like the first picture like you saw here, the brain has to coordinate different parts of its circuitries to be able to figure out what this might be. And by this time this becomes easier for most individuals, but people with schizophrenia might have this difficulty in synthetic thinking that is also a part of the cognitive difficulty in this illness.

So in summary, speed, memory, attention reasoning, emotional recognition or tact, and also synthesis, these are the key elements.

Let me tell you a little bit more about social cognition. When a person, let's say you go to meet your boss and the boss does not seem to be in a good mood, and you need to be able to know whether the boss is in a good mood or not and be able to look at his or her face and figure out emotions. That is what is called emotion recognition. There is another situation in the same situation, not only do you need to figure out what the boss's mood is like, but also what might be causing the boss not being so happy. Perhaps the

boss has had a bad day at home. That requires an ability to put yourself in the other person's shoes and think about the other person's perspective, which is what is called perspective taking, also called theory of mind in psychology circles.

If you go to the next one, the person not only has to figure out what the boss is up to and how he's feeling, but also you need to ask for a day of vacation. How do you do it? So you have to get yourself into a time point where you can actually ask that question and you need to figure out what the social context that boss is in. Find a time when the boss is by himself and has some free time and evaluate the social context. Social context appraisal. This is another component of what we call social cognition. And finally, the person has to mentally put together a way, an account, a narrative in which you can successfully ask and get a yes answer from the boss, as you see here. Just want to let you know we are all fully up to date on the job requirements and I had told you why I need to take a day off and so forth. And this is what is called emotion management. And so that's another component of social cognition.

Why I am saying all this is, all of these are difficulties that people with schizophrenia might experience. And treatment approaches such as what I'm going to talk about, cognitive enhancement therapy, take a way, develop a way of teaching, training individuals to develop that emotional muscle in the brain, if you will.

Now let me switch gears and move to another key part of what I'm going to talk about, which is about brain plasticity. Brain plasticity is a property of the brain in which one neuron talks to another neuron, and as it interacts with the other neuron, the neurons become stronger in their connection. As you see there, that is neuroplasticity. And in other words, if the neurons of the brain is not used, you're more likely to lose it. So the dictum is use it or lose it. Another way of saying that is the neurons that fire together, wire together. Another way of saying it is the neurons that link together, sync together, they synchronize, and that is how the brain is wired in all of us.

And as you see at the top right, you see the way the brain is producing its electrical activity, what we call the action potential. And as the two neurons are connecting, this action potential becomes bigger. And so that is what leads to brain plasticity. The brain, I told you about the muscles and the different muscles that the brain has and training the brain leads to this kind of a growing of the neuronal connections so that they serve you much better. And the same thing I'm showing in the form of the two synapses that are talking, the more they are firing with each other together, what is called coincidental firing, the bigger will be the response of the brain.

So, let me show you in this animation how exactly neuroplasticity works. I hope this would work. So this is how, you see the different synapses as they network with each other. You'll see the rightmost slice of the brain has so many abundant connections, and what you'll see here is two neurons trying to connect with each other. And this is a video micrograph of 36 hours, scrunched up into a few seconds. You can see the two neurons connecting and actually, their connection is getting thicker. So that is the property of neuroplasticity.

This property was well demonstrated over 50 years ago and has been repeatedly shown that animals that are growing up in complex cognitively rich environments, like on the right side, you see these different mice that are around different other mice and also have different objects of different colors and shapes. So their brains as you see above them, are full of synapses compared to the left, where the environment is simple. There are few other animals and then you see less synapses. So environmental enrichment leads to neuronal proliferation.

This was demonstrated by my colleague Alvaro Pascual-Leone, a few years ago at the Beth Israel Deaconess Medical Center some years ago, where he did a very interesting experiment where he took a bunch of volunteers and got them to practice on the piano. A task like a musical note for about an hour every day for five days, Monday, Tuesday, Wednesday, Thursday and Friday. And he mapped the size of the sensory motor cortex in their brains, which perceive these kinds of musical notes and execute these notes. And as you see here, the cortical real estate, if you will, the size of the cerebral cortex region

progressively grew from Monday, Tuesday, Wednesday, and Thursday and Friday, showing that that muscle is growing as you practice. But even more interestingly, in the next set of experiments, he asked them not to actually practice piano but mentally rehearse the same piano task, and you saw the same thing. So it really, really speaks to you about the power of neuroplasticity.

So, many studies, including our own, have shown that reduced neuroplasticity may underlie diminished cognition and may be caused by the synaptic loss that I mentioned to you earlier. It's a complicated slide, but excessive synaptic pruning leaves too few connections and that might lead to reduced neuronal activity and reduced neuronal plasticity.

Let me go to the next part of my talk, which is about cognitive remediation itself. And cognitive enhancement is an approach that is effective and is a comprehensive way of improving functional recovery. So there are many studies now probably over 100 around the world, showing that cognitive remediation works better than treatment as usual in improving community functioning. This is a meta-analysis by Til Wykes, and then we did a meta-analysis as well on social cognition. By and large, most studies have shown that it works.

There are two kinds of cognitive remediation. One is simply to compensate for the problems, the cognitive challenges that the person has been experiencing, the memory difficulties or the cognitive impairment. So simply making up for the deficits by reminders and signs at places of daily activities, having checklists, and bundling supplies for example, if you want to remember to do a particular task, keep it at the place which reminds you. So that's what we call a compensatory approach. It is not actually trying to train the brain itself, but making it easier for the brain. That's one approach. The other approach is actually enhancing cognition by training the brain, and that can be done in two different ways. One is just by practice. Practice after practice, after practice, drill and practice. The other approach takes is what is called strategic approach. My slides are not moving. Let's see.

How do I make it move?

Ken Duckworth:

Hagen, would it be possible for you to take control to see if we could advance these slides, or is this an issue [inaudible 00:34:34]?

Dr. Matcheri Keshavan:

Sometimes if I re-share it, it works.

Ken Duckworth:

Okay, thanks, Kesh.

Dr. Matcheri Keshavan:

Yeah. Let's try this now. So now it works.

So this cartoon really gives you the idea of the compensatory approaches, full of reminder notes as this person walks in and out. So that's the compensatory approach. The restorative approaches uses, as I said, repeated practice, drill and practice, to not only improve neurocognition but also social cognition.

Traditionally, over the initial few decades of this line of work, we were using simple things like a paper and pencil, crossword, and brain-teasers, and Sudoku and so forth, which are still useful. But more and more there are online approaches available for this kind of brain practice, practice of attention, memory, and executive function and so on. So there are many such online programs available, and I have a few names here of the more popular ones. One approach is called Lumosity, which has hundreds of exercises, which is useful. And it costs a little bit of money, it's about \$70 per year as I last remember it. Then there's another one called PositScience, which is now has got a new name called Brain Headquarters,

Brain HQ. Then there is another one called Happy Neuron, and so forth. PSSCogRehab is another one and so on. So these are online practices.

But one point I want to say, and I think Kim Mueser may have said this before as well. Simply doing this kind of practice on a computer is not enough to produce benefits. You also need a therapist or a coach. Coaches can take the individual through thinking skills themselves, which is what you would've heard last time, some of you who went to Kim Mueser and Susan McGurk's talk. Strategic thinking requires not only neurocognition but also what is called metacognition, that is thinking about thinking itself. Metacognition refers to understanding one's own cognitive strengths and limitations, and also to be able to think about strategies of how to make thinking easier, thinking about, what is it that I can expect from this situation? What is it that I can do or what is it that I cannot do? And what is it that's likely to happen if I did it this way versus another way? And so on. So that is thinking about your own thinking.

Another important aspect of strategic thinking is helping individuals to get the big picture, of getting the gist. Remember I pointed out that one of the key elements of cognition is the ability to get the big picture by filling up the blanks in our own mindset and so on. So also, individuals need to know that they don't need to pay attention to everything. They don't need to pay attention, remember everything. In fact, trying to forget something is an actual skill. So in our training sessions, we get people to exercise with complex paragraphs and get them to point out what is the gist of it in one sentence and so on. So the ability to separate the important point from what might be not so important and so on. So that requires a training skill.

And the other thing is to be able to think outside the box. And on the top right you have this simple example of how to think outside the box. If you are asked to draw a line through three Xs on a piece of paper, and here's the way of doing it outside the box metaphorically, so to speak.

Another important aspect of thinking is what we call growth mindset. There are two kinds of mindsets that is widely known nowadays, and one is where you really begin to think of yourself as either smart or not smart. And that is a fixed way of thinking, thinking about something you'll never be able to do it is a fixed mindset. But on the other hand, individuals who think of thinking as a growth process, oh, I might have made a mistake, maybe my mistake will help me better next time. So, and keep doing it in a way that you are growing from test to test. That is called growth mindset. That's another important thinking skill.

So, practice is critically important. And also thinking about the other person's perspective. What is the point of view of your mother in that situation? Why do you think he got upset with you? How can you let her know what you're thinking or feeling? What benefits would that have? So, helping the individual to think about the other person's perspective. So in this cartoon, if you want to put yourself in the other person's shoes, you'll see that the number for the left side person is not only a six, but could also be a nine from the other person's perspective. So this approach, what is called theory of mind, helps the individual to take the other person's perspective.

All of those were combined in this approach, which we call cognitive enhancement therapy, which was developed by my mentor Gerry Hogarty, going back almost 25 years. He's no more, unfortunately. And he put this package together, whereby we help the individuals to first learn ways of managing one's own stress, identifying symptoms, learning relaxation techniques and so on, through individual psychotherapy, coaching. Followed by computer-based exercises, neurocognitive remediation, which involves attention modules, memory, and problem solving modules. And we do it in pairs. Two people with the illness get together and they develop a collaborative approach and solve computer-based exercises with a coaching by the clinician. This is in a one way, combining neurocognitive remediation with also developing social cognition by learning to collaborate, learning to criticize in a constructive way, learning to learn from mistakes and so.

And then we have in parallel groups that focus on social cognition, where we take the group individuals, participants through various aspects of social cognition, metacognition and so forth, using exercises. Both homework exercises, as well as exercises in groups themselves, about how to act wisely in social

situations, how to appraise social context, how to take the other person's emotional temperature and so on. These are one and a half hour group sessions for a total of about 45 sessions. We are able to do that now in one year. We're developing at this time a six-month version of this as well. So there are three components, individual coping, computer exercises, and group exercises.

Now, we have done three independent trials, first in a chronic schizophrenia study, and then in an early course study, and then in an independent early course study again. So all of those have shown that cognitive enhancement therapy is better than treatment as usual. And we also found that when followed up, even after the end of the treatment, the effects were persisting, the beneficial effects were persisting, and I'll show that in another slide. We scanned individuals before and after receiving the intervention, and we found that some of the gray matter reductions that we had seen at the beginning were actually reversed in people who were treated with cognitive enhancement therapy, compared to those who received supportive therapy alone. So it is not only improving cognition but also protects against gray matter loss. The more the brain changes, the larger was the improvement in cognition.

So this is our durability data at the end of three years, on the left side. And so even after the end of the treatment, the beneficial results were persisting, and another study showed the same thing in the early course of schizophrenia. And more recently an unpublished study showed that even at the end of 10 years, about eight years after the end of the treatment, they were still showing beneficial effects. And individuals who received cognitive enhancement therapy were more likely to be employed. Paid employment compared to enhanced supportive therapy that was our control intervention. And there were also beneficial effects and negative symptoms, anxiety and depression, but these were all stable individuals when they entered the treatment. So we didn't have much, we didn't predict much effects on positive symptoms as we expected.

We have also published data showing that a very similar approach works in autism. Shaun Eack has been the leader in this field from Pittsburgh, and Ian Lewandowski has used a similar approach in bipolar disorder with psychosis and has reported beneficial effects. And Vandana Shashi in North Carolina has tested this approach in individuals with intellectual disability with 22Q deletion syndrome, and it works there as well.

Now, some new directions. First of all, early intervention. And we have, as you saw in a couple of independent controlled trials, we have found that early intervention with cognitive remediation in individuals whose illness has lasted less than a few years is quite effective. So if cognitive improvement is likely to improve opportunities in life, why not use them early? So that is the approach that we have taken. And even in the individuals who have not yet developed full-blown psychosis but are in what we call the prodromal phase, that is those with milder symptoms the few months or years prior to the onset of the illness. Michelle Friedman-Yakoobian in our group has shown that cognitive enhancement therapy's six-month version of that has shown to be beneficial.

The second thing that increasingly the literature is pointing to is that physical exercise itself improves cognition. And so at this time we are trying to combine cognitive exercises with physical exercises in a virtual reality-based approach. And we have in a very preliminary way, shown that this kind of a combined physical exercise and cognitive exercise can be effective in improving cognition.

Sleep is important. You all know that we remember things better when we sleep over it, and especially if we sleep well. And we have found in our group, with Bob Stickgold and Dara Manoach at Mass General and at Beth Israel, that this property of the brain to consolidate our memories when we get a good night's sleep, is because of a particular kind of oscillation in the brain called spindles, sleep spindles, because they look like spindles. Now sleep spindles, the more there are the better for cognition. And we have shown that people with schizophrenia, have very little sleep spindles, and may be the reason that they don't remember things overnight and their sleep is also not very good.

So at this time, we have an ongoing study led by a psychiatrist resident by the name Michael Song and Tony Cunningham, a sleep expert, to see whether we can actually improve memory consolidation by

getting individuals to take a nap in the afternoon and stimulate their brain using a very safe brain stimulator called transcranial direct current stimulation, and actually induce these spindles, and sleep spindles could enhance memory. So this is another very, very interesting approach for the future.

John Torous in our group has been developing a way of building cognitive remediation approaches just on your smartphone itself. There is a software program, it's an app called LAMP that he has developed, in which there are cognitive exercises. So if the person has some free time waiting for a bus or something like that, he can do some trail making test right on the phone while you are spending time waiting for a bus. So that is another way to make the best use of time during the day to keep exercising the brain.

Another important aspect of improving cognition is to know who are the people that are most likely to need cognitive remediation. In our group, we are identifying subgroups of psychosis, irrespective of their psychiatric diagnosis, whether it's schizophrenia or bipolar. They fall into three different subtypes. One particular subtype, which we call biotype one, is the cognitively most impaired subgroup. It may be that that is the group that most likely requires and benefits from cognitive remediation. Biotype one, as well as biotype two in our more recent work.

And Roscoe Brady in our group has been conducting a study to see whether brain stimulation, which is using another safe approach to neuromodulation or brain stimulation, called transcranial magnetic expansion, whether that can enhance connectivities in the brain, and thereby improve cognition. So this is still work in development and he has already shown that it improves negative symptoms, but the question of improving cognition is to be determined.

And finally, can these kinds of approaches be implemented in community settings? We're in the process of completing a large comparative trial funded by the PCORI, patient centered... It's a grant mechanism funded by the SAMHSA. Shaun Eak is in this picture. Kim Mueser, whom you have heard last time is here. So in this collaboration, we are actually implementing cognitive enhancement therapy across nearly about 18 sites around the United States. And we are about to finish that study, and our goal is to compare these interventions with another approach, social skills training, that Kim Mueser is leading. And over the course of the next few months to years, we'll have an idea as to which one is better and which one works better for which kind of people and so on.

So my take home points are, first of all, cognitive deficits in schizophrenia are pervasive across the different domains of cognition. They're persistent during the illness, they're present early and they may progress early, and they also predict disability. These deficits are related to synapse loss and reduced brain's plasticity. My second point of my summary is, the brain has a remarkable ability to build itself or repair itself, and this phenomenon of neuroplasticity is impaired in people with schizophrenia. My third key point is that cognitive remediation approaches, such as CET are effective and generalizable and durable. They can be used early as well as chronic.

And finally, cognition can be enhanced by improving physical activity, improving sleep, certain medications perhaps, which again, I haven't gone into details of the medication. One thing we have found over the years is that there are some medicines that are bad for cognition, and these are anti-cholinergic medicines. Medicines like Cogentin, for example, unless they are needed to treat Parkinsonian-like side effects, one should minimize the use of those because they actually are bad for cognition. So, medication subtraction actually might help in some individuals. Keeping it simple, talk to your doctors, and what is it that can be reduced or minimized?

Certain brain stimulation approaches may be useful and smart devices are being developed to have cognitive exercises built in them. And cognitive remediation approaches can be implemented in the community settings, and biomarkers down the road may become available to select who might respond best to which kind of approach to treatment.

So, I want to thank many individuals, especially NAMI, because the Peter Corbin endowment gave me some money, which I have actually used for further studies of cognitive remediation. And these are my other grants that have supported. Thank you, we are very grateful to the patients and their family

members who have participated in our studies. And those who want to ask me questions, my email is [here](#).

Ken Duckworth:

Thanks, Kesh.

Dr. Matcheri Keshavan:

[inaudible 00:55:23].

Ken Duckworth:

Terrific talk, we have a lot of questions. Let's talk about the most common question, which is, where can people find cognitive enhancement therapy? There's one person who said, "My son benefited from this greatly. When the grant run out, we couldn't find it through Medicaid." So should people look at academic centers? Is there a clinical trial site? Because I think it's pretty well established this framework is helpful.

Dr. Matcheri Keshavan:

So, it is established to the extent that SAMHSA has certified it as an evidence-based treatment and it is reimbursable and all that. So, there are a number of academic sites and some non-academic sites which participated in our PCORI studies, and we are in the process of discussing with them how they can implement it in a non-research way going forward. So some of them have expressed a great deal of enthusiasm in that, and so it might be possible. So, any of you who are interested, please write to me and see that we could point you in the right direction.

But there's also a program in Cleveland that does train different site settings for cognitive enhancement therapy around the country. That's called the PLAN program, P-L-A-N, and so that's worth looking into, and there are other-

Ken Duckworth:

[inaudible 00:57:00] question.

Dr. Matcheri Keshavan:

... cognitive enhancements. Some of them are available, as I said, online approaches are available as well. If a actual clinical program is not available in your area, you could get onto an online program as well, and so on.

Ken Duckworth:

Kesh, questions have come up about schizoaffective disorder, bipolar disorder with psychosis. Have those been studied-

Dr. Matcheri Keshavan:

Yes, yes.

Ken Duckworth:

... using cognitive enhancement? And what would you say about that? Is the same set of strategies beneficial for people who have these kind of overlapping diagnoses in the Venn diagram?

Dr. Matcheri Keshavan:

Now, increasingly the field has learned that people with bipolar disorder also have cognitive difficulties similar to schizophrenia but sometimes lesser in magnitude, and schizoaffective disorder is somewhere in between. We have published results showing that cognitive enhancement therapy works for schizoaffective disorder. Ian Lewandowski at McLean has shown that an approach similar to cognitive enhancement therapy that involves computer-based exercises plus what we call bridging groups, similar to the CET groups, works effectively in people with bipolar disorder with psychosis. So, there is a fair amount of data now.

Ken Duckworth:

So Kesh, this new medicine that's come out, Cobenfy. I know that's not the central aspect of your talk, but it is a different mechanism of action. You mentioned anticholinergics and the problems related to that. Do you have thoughts about that as an adjunct [inaudible 00:58:47]?

Dr. Matcheri Keshavan:

The reason why there is some enthusiasm for Cobenfy for cognition is that, I told you anticholinergics are bad for cognition. By corollary, think of cholinergics being good for cognition. In fact, in Alzheimer's disease, there are a number of cholinergic agents that are useful and are in practice. So Cobenfy, which is called Xanomeline, combined with a drug called Trospium, was first used in Alzheimer's disease for that matter, going back about 15 years or 20 years. And it was actually found to paradoxically benefit psychosis in people with Alzheimer's disease. So it was given up because it had peripheral side effects like nausea and vomiting.

So cleverly, Cobenfy came up by combining this Xanomeline with a peripheral drug to block astral choline so that the peripheral side effects could be diminished by Trospium. And so that combination is now approved for schizophrenia. It is not approved for cognitive impairment. However, there are some early results that are published just a few months ago, maybe a few weeks ago, showing that it had a benefit for cognition. So, more to learn. We'll definitely see a lot more literature on that. So it may-

Ken Duckworth:

So it's an early hint.

Dr. Matcheri Keshavan:

It's an early hint.

Ken Duckworth:

It's not a FDA approved construct. Couple other questions. Use of marijuana in cognition. What is your perspective on that?

Dr. Matcheri Keshavan:

Well, marijuana does not have any beneficial effects on cognition. There are studies which do show that it may in that of itself, impair cognition. So that field is a little bit controversial at this time. In our own data, we find that people who have psychosis but also use cannabis, tend to have somewhat better cognition. So, one might say that this is protective for cognition. But the other approach, other explanation for that is that these are people who have a milder psychosis which was triggered by the cannabis. Simply because it was a milder psychosis predisposition to begin with, they may look like they're more cognitively spared. So we don't know whether cannabis is actually protective in any way. We don't think it is. Studies have not actually confirmed that.

There is one line of work that is, again, somewhat debated as to whether one particular ingredient within cannabis called cannabidiol or CBD might have a beneficial effect. But again, there are mixed studies, mixed reports. One study showing beneficial effects, one study not showing that.

Ken Duckworth:

Would you agree early use of marijuana raises risk for psychosis?

Dr. Matcheri Keshavan:

Yes. Yeah, that seems very clear.

Ken Duckworth:

That complicates this question. So, a couple things. People want to see your email address again.

Dr. Matcheri Keshavan:

Okay.

Ken Duckworth:

And people want us to remind them of the medicine. It is spelled, C-O-B-E-N-F-Y, Cobenfy, and this is the cholinergic-based medication. Here's the good Dr. Keshavan's email, and he was very generous in saying he would try to direct people to programs.

What do we know about the ketogenic diet? It is interesting to me, but I haven't seen a lot of randomized controlled trials on cognition. We are going to try to get a speaker on this. We've interviewed a few people for a future SE expert as this literature gets more developed. Do you have thoughts about that?

Dr. Matcheri Keshavan:

Yeah, I'm not an expert, obviously, but my understanding is that the results are based on either small studies or an anecdotal case report kind of studies. It might work, but I suspect that... I've seen some patients who have been on it, some it has worked and some it has not worked. It's possible-

Ken Duckworth:

For cognition or for psychosis?

Dr. Matcheri Keshavan:

For psychosis.

Ken Duckworth:

Okay.

Dr. Matcheri Keshavan:

For cognition, I don't think we know much at all, but even if it does work, it may work in a small segment of the population. You all know that schizophrenia is a heterogeneous condition with probably, it's a mix of multiple disorders. There may be a biochemically distinct subgroup where there are alterations in their metabolic pathways, that there might be a particular subgroup that might benefit from the ketogenic diet kind of thing. Again, I'm not the expert, so.

Ken Duckworth:

Yes, but we're going to try to have that conversation as this literature develops. We're following that. We're interested in it because interested in all things that might help people.

A question comes up, a woman has a 27-year-old son who's been ill for about a decade. Is it too late for cognitive enhancement theory to make a difference?

Dr. Matcheri Keshavan:

Absolutely not.

Ken Duckworth:

So the key is to get to it, though, right?

Dr. Matcheri Keshavan:

Yeah, [inaudible 01:04:57].

Ken Duckworth:

That sounds like the key.

Dr. Matcheri Keshavan:

Yes.

Ken Duckworth:

Would you say most of these programs are in academic centers or not so much?

Dr. Matcheri Keshavan:

Most of them are in academic centers, yes.

Ken Duckworth:

Okay, so if you live in Oklahoma, that's the University of Oklahoma, Department of Psychiatry or Psychology. If you live in Alabama, I mean, if you live in Atlanta, that's be Emory University. Right, again, so you're looking for the big academic centers, and then you're looking for people in psychology and psychiatry who are doing this work, because not in typical community mental health at this point. Would you agree with that?

Dr. Matcheri Keshavan:

Yeah, that is true, yeah.

Ken Duckworth:

Okay. Now, if you're in community mental health and you can't get to Emory or Tulane in New Orleans, how about doing this online with other people? So you're in a group and you're working the problem together, as opposed to just doing the online idea. Do you have a sense of how effective that is, Dr. Keshavan?

Dr. Matcheri Keshavan:

Yeah, so that's a good question. And in our own PCORI-funded study, we did cognitive enhancement therapy remotely, entirely remotely in force in two sites, and compared that with the two parallel sites,

who got the in-person approach. And we compared them and there were not too many differences. So it does work even remotely. So remote interventions are possible, especially for computer-based exercises. And the groups also, it's possible. There may have been some advantage of in-person group attendance, but it is doable even remotely. And in fact-

Ken Duckworth:

Couple quick-

Dr. Matcheri Keshavan:

... discussed with various sites about implementation after the end of this study, they all favored moving towards a remote approach.

Ken Duckworth:

Couple of questions have come up about schizoaffective disorder again, and have you found that it's just as effective?

Dr. Matcheri Keshavan:

Yes, it is just as effective. With our own results, we published a paper on that as well. There was no difference in the efficacy between schizoaffective and schizophrenia.

Ken Duckworth:

A couple questions about work, and I'm going to encourage people to listen to Susan McGurk and Kim Mueser's talk a month ago. So Dr. Keshavan's talk is part two of cognition, and they actively discuss work, thinking skills for work, and then how to apply things at work.

Kesh, we're big fans of clozapine, which we believe is an underutilized medication, and I testified along with many other people at the FDA to try to make clozapine more accessible by reducing some of the restrictions of REMS. NAMI's official position is that people should be allowed to opt out, particularly after a certain period of time and make their own decisions about risk. Do you have a take on clozapine and cognition?

Dr. Matcheri Keshavan:

Well, studies so far have not shown a cognitive benefit in people with schizophrenia. I say that with a caveat. There are some people whose cognition is impaired secondary to unresolved psychosis. In those individuals, clozapine gives them a break from psychosis so that then they can participate in cognitive enhancement programs. So in that way, clozapine does have a value.

Ken Duckworth:

Last question. Let's talk about video games, musical stimulation, other kinds of brain type strategies that people use in ordinary life. Have they been studied or is it important to do a more formal cognitive enhancement training concept?

Dr. Matcheri Keshavan:

Yeah, so doing video games or computer exercises in and of themselves are not as effective-

Ken Duckworth:

Not, okay.

Dr. Matcheri Keshavan:

... as combining them with the clinical coaching. That's been a general consensus among many studies, including Kim Mueser, who has published on that.

Ken Duckworth:

Excellent. Well, Dr. Keshavan, We had 650 people on this call to match the 650 people we had with Susan Mueser. That's 1,300 people who care about cognition. We're going to stay on this as studies come out about cognitive enhancement therapy, plus this new medicine perhaps. That's an obvious opportunity as we learn more about the ketogenic diet and its potential impact on cognition, psychosis, that's another opportunity. And as the FDA rules on REMS and access to Clozapine, that's another opportunity. So we may invite you back. We appreciate you very much for the work you're doing, and I want to commend people to the more than 60 webinars that we have with some of the smartest people really in the world on mental health conditions and serious mental illness topics of interest. Let's go to the next slide. Dr. Keshavan, thank you for everything. We're going to do a couple closing slides, but I really do appreciate everything you're doing.

And so, we're going to do one on weight gain that comes with anti-psychotic medications. And as you know, there are new medicines that have been promoted and FDA approved to help with weight loss. This is the first time we've ever had this talk on these new compounds and the weight gain associated with anti-psychotics. Then another friend of the family, Dr. Maurizio Fava, the Chairman of Psychiatry at Mass General Hospital, will be discussing treatment resistant depression. Dr. Fava has written hundreds and hundreds of papers on depression and treatment resistant depression. So Dr. Jonathan Meyer, Dr. Maurizio Fava, this is an all-star team that we have in January and February. I hope you can attend. Next slide, please.

Here's our book series. Book number one, which Dr. Keshavan is in, describing the coordinated specialty care model, is a USA Today bestseller, and *You are Not Alone for Parents and Caregivers* recently came out, by my colleague, Dr. Christine Crawford. We now have a buy one get one free, if you look around on the NAMI website or NAMI communicate, you'll find it. And that'd be a fun holiday present. All right, next slide please.

We have sponsors, here they are. The sponsors do not have any impact on the content of our work, but it won't surprise you that to run a webinar series for free does take support of other parties. Next slide, please.

You are not alone. This is an informational webinar. This is not medical advice, per se. This is to up your game in understanding where to look. If you enjoyed this program and you want to be kind of our own little mini sponsor, consider donating to keep this program alive and well. Next slide, please.

I want to thank you for joining. Dr. Matcheri Keshavan is one of the leading experts on planet Earth on cognition and what we can do about it. If you have any questions for me, I'm ken@nami.org. I have an agreement with HR, a rather informal agreement, that no one named Ken can work for NAMI so that I can continue to have this vanity license plate type address. If you have suggestions for future topics, asktheexpert@nami.org, will go to my colleague, Hagen, who is our Executive Producer and began this seminar.

So I want to thank you for your attention. Thank you for all you do to support NAMI and our shared mission. Dr. Keshavan, have a wonderful holiday season and thank you once again.

Dr. Matcheri Keshavan:

Thank you.

Ken Duckworth:

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Good bye, buddy.