University of Manitoba: "What's the Big Idea?"
Series 4, Episode 5: DR. ZAHRA MOUSSAVI

TITLE
Unlocking Brain Resilience: Non-Pharmaceutical Interventions for Alzheimer's and Dementia

INTRO MUSIC FADES IN

INTRODUCTORY MONTAGE

Media clip
https://www.youtube.com/watch?v=IMPPqkCivWQ :
"A new report from the Alzheimer's Society of Canada predicts that nearly 1 million people, here in Canada, will be living with dementia by the year 2030. So, that's more than a 65% increase from the number of us living with dementia in 2020."

Zahra Moussavi
"I firmly believe that, at least for Alzheimer's, yes, we can slow the progression, we can stabilize, and maybe we can even improve, if we have the patients at the very early, early stage."

INTRODUCTION

MICHAEL: Welcome to What's the Big Idea? I'm your host, Michael Bennaroch, President and Vice-Chancellor at the University of Manitoba. By 2030, researchers project that nearly 1 million people in Canada will be living with dementia, mostly Alzheimer's disease. Despite the need, pharmaceutical interventions for dementia are known to have significant side effects and minimal benefits. This can make a diagnosis feel hopeless.

But what if there was a way to intervene without pharmaceuticals? What if we could do something that would reignite patients' brains and bring them back to themselves? My guest today believes we can, and her research backs her up. Zahra Moussavi is a Canada Research Chair in biomedical engineering and a professor in the Price Faculty of Engineering. Her unique research focuses on non-pharmaceutical interventions for Alzheimer's and dementia. She has published over 360 peer-reviewed papers, received numerous awards, and ran the largest clinical trial of its kind to test her ideas. Her results? More than 80% of participants improved significantly, right after the intervention. Stay tuned. Moussavi's ideas are ones you won't want to miss.

MUSIC FADES OUT

MAIN INTERVIEW

MICHAEL: Your big idea is that we can halt and sometimes even reverse Alzheimer's disease with non-pharmaceutical interventions. But before we get into the science of this, let's talk about what's happening right now, in my brain. I'm about to learn something new from you and my brain is going

to change. Tell me more about what's happening in my brain.

ZAHRA MOUSSAVI: Right at this moment, in your brain, in my brain, there is a magnificent firework. Trillions of signals, action potentials are being generated from different parts of the brain. And we are talking about your brain, my brain. We are talking about something new, maybe the dominant frequency of the waves would be in gamma-band. Gamma-band is a range of frequency between 30 to let's say 80 hertz. Everybody has a slightly different gamma frequency. Yours could be 42 hertz, mine could be 39 hertz, but it is that range that is dominant. And that's the bandwidths or the wave that our brain generates when it is focusing, learning something new. And in fact, that is our goal too, to boost activity in the gamma-band so that it leads, eventually, to neuroplasticity in Alzheimer's brain. Which parts of the brain are being activated? For sure, the auditory system is activated and both left and right, as well as, definitely, prefrontal cortex, the boss of the brain or hub station of the brain because it has projection everywhere else. All in all, they are creating a magnificent firework.

MICHAEL: Well, that's amazing. Most people don't think my brain is firing, so. So now, how would this differ from somebody with dementia? What would their brains look like, and what would be happening in their brains, at this time?

ZAHRA MOUSSAVI: Depends on the stage of dementia. At the very earliest stage, probably even the best fMRI doesn't find anything different. It is still a firework because remember that we have trillions number of 30 trillion synapses. Not all of them are being activated at the same time, but millions for sure, if not billion. So, at earliest stages, probably we won't be able to discern the subtle changes, but at moderate stages, the activity of the brain could become chaotic, and at advanced stages, it will become silent. So yes, there is a difference in that firework characteristic, that is in the brain, but whether we are capable of registering it, finding the differences, at earlier stages probably not. But at moderate and also advanced, yes.

MICHAEL: And so, you said it wouldn't be firing.

ZAHRA MOUSSAVI: At the very advanced stage, it mainly can be considered silent. It is firing but not much, because most of the synapses are faulty and broken and the neurons, therefore, are not communicating. The way that we perceive things, the way that we act or say something is by communication between different parts of the brain, and this communication happens through the channels called synapses. If those synapses are faulty, broken, then there is no communication. No firework can continue from one neuron to another.

MICHAEL: And so, how would you use this information in your treatments? I know you've been working on this for quite a long time. How do you use brain waves to make a difference in people experiencing dementia?

ZAHRA MOUSSAVI: In Alzheimer brain, we know that probably some neurons are dead. Basically, the grey matter volume has become less. For the neurons that are dead, we cannot do anything. We cannot bring them back to life. But before that happens, it is mainly some of the synapses, some of the channels between the neurons that are being broken, because of the accumulation of tau

protein and excessive beta amyloid. So, those tangles and plaques sit on the synapse and doesn't let the signal to go through. Okay, but we have a lot of synapses. We have quite a lot of redundancies. And our goal is by stimulating the brain, by two means simultaneously, we help those existing synapses to work better, and we know that if the neurons are fired together, they wire together. So, we are hoping that maybe we can even generate new synapses to replace the faulty synapses.

MICHAEL: I was reading about your background and how you got into some of this research. My mother suffered from dementia. And your mother, years ago, was diagnosed with Alzheimer's, but long before the official diagnosis was made, you knew something was wrong. Can you tell us this story and how it shaped your research career? And what happened that drove you, as an electrical engineer, to become a leading thinker in this field?

ZAHRA MOUSSAVI: Sure. As you said, I was a happy electrical engineer and my expertise was, still is, in biological signal processing and I was working on a swallowing disorder, respiratory disorder, sleep apnea and those areas. I still continue on those areas too because I like signals, in general. The first time that I noticed something was wrong, in my mom, was year 2000 when she came to visit me with my father. Mind you, my mother was in Iran and I was in Canada. And I hadn't seen mom for five years. And I noticed a significant change in mom, in her vocabulary, in her spatial awareness, in particular that caught my attention. So, I took her to the best neurologist in town, in Winnipeg and she passed that MoCA test that everybody runs at the very first screening, and she aced it because mom was a very educated, intelligent woman and she could disguise her problem easily. I wasn't convinced that mom didn't have any issue. That year passed. She came back in 2001 and again I took her to the neurologist. Again, I was told that I was imagining and mom was okay. And she was finally diagnosed in Washington, D.C., where my siblings are, in 2004. But by 2004, it was pretty obvious, and then, from 2002 or 2001, I started to educate myself in Alzheimer's. I knew nothing in neuroscience, so I had to start from scratch. And basically, educated myself in neurophysiology, a little bit, and Alzheimer's disease. And I started to put my observations together, to come up with a technique that can detect a neurodegenerative dementia. At that time, I thought I was detecting Alzheimer's. At the very earliest stage, before clinical symptom becomes evident, because as I said, I noticed in year 2000, and she was diagnosed in 2004. That's how it started. And in fact, my test at the time, I call it egocentric spatial assessment with virtual reality. And since 2010, I have tested it on more than 400 older adults and more than 200 Alzheimer patients. And I have a faith on it. It can raise a warning flag, at least about two years prior to clinical symptom. Initially, I thought it is only detecting Alzheimer's, and now I know that it is not only Alzheimer's that can raise a flag. It can detect a neurodegenerative dimension, except frontotemporal dementia, because those people are good spatially.

MICHAEL: That's interesting. And a lot of us who have had parents or friends go through dementia know that, at the early stages, they can cover it up. With my mother, what used to happen is she would have an afternoon nap, and she would wake up very confused and she would say to us, I forgot everything but now I'm remembering it again. And of course, we just thought she was coming

out of sleep but in fact, very similar to your mother, it was probably very early stages. So, testing it early is obviously important. And so, do we have better tests now?

ZAHRA MOUSSAVI: Better in terms of definite diagnosis, no, there is no single test that can definitely diagnose. They say that the true diagnosis of Alzheimer's occurs post-mortem, by a brain autopsy. Because we know that it is not excessive beta amyloid that really one gets Alzheimer's. For a number of years, they thought that that was a determinant of the Alzheimer's. Now we know that it is not. Now we know that excessive tau and beta amyloid lead to Alzheimer's, sure, but none of these have enough sensitivity to detect at earlier stages. I'm not claiming that my test is also definite in determining. I'm just saying that it is raising a warning flag to watch a person. Over the years I have had about eight, nine people whom I was able to follow up over five, six years and they developed Alzheimer's. There is lumbar puncture and measuring the amount of beta amyloid and tau, in the spinal fluid that definitely is a good diagnostic test. MRI at earlier stages doesn't have that sensitivity. PET scan can help. All of these are called diagnostic aid. And we have also another test, by the way, electro vestibulography or EVSG for short. This one also is a diagnostic test. I believe multiple approaches, parallel approach, diagnostic aid collectively, yes, they can detect dementia, particularly Alzheimer's at the earliest stage. And the earlier we detect, the better. The earlier, the better because then the treatments are effective.

MICHAEL: So, in your labs, you've pioneered virtual reality navigation tasks, for early detection of Alzheimer's. Could these immersive technologies be used not just to diagnose, but in some way rewire or restore memory circuits in the future?

ZAHRA MOUSSAVI: That would go into the field of neurorehabilitation. My virtual reality navigation test, I used it once on a gentleman. I am allowed even to say his name, John Robson. He has been with us since nine years ago. The very first time that virtual reality navigation test raised the warning flag about John. So, I called John back in six months and then another six months, three times. And his error score increased, so, I told the wife that I'm afraid that John is developing Alzheimer's. At that time, he was not diagnosed with Alzheimer's, even by the specialist.

So, we enrolled him in the same virtual reality navigation test, but as a neuro rehab. One of my students actually did that. And it was the very first study on its kind, the very first paper, and that's why it has had a lot of citation. We showed that if by working repeatedly, in the virtual reality environment, just on spatial awareness, John became perfectly zero error, in that test, after two months. So, he improved. Mind you, we only worked on his spatial cognition. Later on, we enrolled him in other treatment programs. There are many non-pharmaceutical treatment programs. I run a few of them and I believe they are effective, if they are being applied at earlier stages.

MICHAEL: So, in some ways, it may be possible, to stop the brain from slipping into pathological dementia. So, how would we do this?

ZAHRA MOUSSAVI: I know that it is a big claim, but I think I have had enough data, longitudinally, that I firmly believe that, at least for Alzheimer's, yes, we can slow the progression, we can stabilize, and maybe we can even improve, if we have the patients at the very early, early stage. How we can do it, I have tried RTMS, repetitive transcranial magnetic stimulation, which is the coil over the

head, zapping the brain and so on. That was the largest clinical trial in the world that we ran, in Winnipeg with McGill and Monash in Australia. Then, in parallel, I also applied electrical stimulation, either DC or AC, at different frequencies. And my results of 73 patients, longitudinally, these patients have been loyal, come back every few months for treatment, which has recently been published. Over three years' data that we published, it shows that, yes, we have been able to stabilize the condition, and patients did not decline as it was expected.

The interval between the treatments were between two to six months. And we also showed that statistically, the larger interval, the larger gap, no treatment period, were associated with more decline. That's why that I'm claiming, if we do it on a daily basis, with no interruption, yes, we can stop the progression.

MICHAEL: I find this fascinating. And so, interventions then seem to be the key. And this is where your big idea comes in, right? So, you're talking about every day. And so, you have this vision of running a centre that can provide treatment and interventions that could do this work and potentially either slow down or reverse. What's your vision for equitable access to cutting edge dementia care?

ZAHRA MOUSSAVI: I envision this centre to be running every day, for six hours a day. It's like an older adult school, dementia school, you may call it. Not the entire six hours I would give treatment, but I would give treatment for two 30-minute sessions. And these treatments would be personalized and optimal. What we do, right now, is that we measure the EEG of the patient, at every baseline, every time that they come for treatment. And then we apply the electrical simulation at the personalized Gamma, personalized Theta bands and see the effects. In such a centre, I would determine that optimum frequency of the treatment. And would treat every patient, on a daily basis, with that personalized treatment. And then, for the rest of the day, we will have different activities. We can have gardening, we can have crafting, we can have all different games that stimulates the brain. And mind you, social interaction between people is also the key for keeping them active.

MICHAEL: So, keeping the brain stimulated.

ZAHRA MOUSSAVI: That's right. Reversing is a huge claim. I'm not confident to make that claim. But I believe if we do this, yes, we may slow the progression. Because brain is really like a plastic. We can stretch it. We have trillions number of these synapses. Some synapses break down. Okay, fine, we can use other synapses to take over the job, or we can even regenerate new synapses.

MICHAEL: So, you mentioned that you're not comfortable saying it would be reversed, but it appears as if your research is showing a lot of promise that Alzheimer's and related dementias can be managed more as a chronic, possibly treatable condition instead of inevitably a progressive one, right? So, we can think of this with lots of diseases, right? So, you have high blood pressure, you manage it with a drug that works, but you stop the drug, you have the high blood pressure. So, you manage it as opposed to inevitably having it get worse.

ZAHRA MOUSSAVI: That's right, and I'm glad that you mentioned it because there is also a new way of treatment that made me very excited. Just in case if I get Alzheimer's, I would definitely follow up

with that treatment. This treatment has been found by accident, in China. Dr. Li was doing a lymphatic surgery, basically putting a shunt in cerebral lymphatic vessels to treat tinnitus and headache in a patient who also was having dementia. And after the surgery and reconstructing the cervical lymphatic vessels, the patient became significantly better, in terms of cognition. So, they started doing it, on a small sample, six more patients with dementia. And it seems that in all of them, this shunting the lymphatic system is helping. And it makes sense to me neurophysiologically, because, yes, if the lymphatic vessels are occluded, obstructed, then the toxic of the brain, like the tau proteins, cannot get out of the brain. And if you put a shunt there, then it releases.

Now you may ask how many Alzheimer's patients have this issue. We don't know. Nobody knows because the research is at infancy stage. But I'm hoping that in the near future we will know a lot more about it. In South Korea also at the moment, they use high resolution ultrasounds to figure out if there is such an obstruction and then do the surgery for the patients. There are studies on mice, also in parallel, to investigate the same thing. And so far, the results are quite promising.

And you spoke of blood pressure. In fact, high blood pressure is a major killer and the major lead of some cognitive impairment in older adults, as well. And in fact, the way that our treatment is effective has all to do with the blood flow because our treatment changes the hemodynamic responses of the brain. It changes the metabolism of the brain and helps to increase the blood flow. If you increase the blood flow in the brain, it may even help with the obstruction of the lymphatic vessels too. So, one key lesson here is, first of all, keep the blood pressure low because it can lead to cognitive impairment too. And that may explain actually the mechanism of some treatment, as well.

MICHAEL: So, it seems like there may be different causes of dementia. You talked about the lymphatic system and that your treatment may be able to slow it down or maybe even make it a chronic disease instead of something that progressively gets worse. So, how does this connect with drug trials? I think there's been a lot of different drug trials. They haven't seemed to be that successful, at this point. But is it maybe, again, that the drugs are given too late? What are some of the challenges with the drugs that being used?

ZAHRA MOUSSAVI: First of all, why drugs do not have that effect on the brain neurodegeneration. This is because we have a mechanism called a blood brain barrier that is for protection of our brain, for the toxic not to reach the brain. But this blood brain barrier, BBB for short, also blocks the medication not to reach directly the brain. That's why, in recent years, there has been some research to open up the blood-brain barrier by ultrasounds, but I've heard from some respected neurologists that there are some doubts that you open blood-brain barrier. Are you sure that after four hours it closes down completely? Because a leaky blood-brain barrier has been also correlated with neurodegenerative dementia, as well. A leaky blood-brain barrier can also let some toxics to get to the brain. The leak is not big enough for medication to go through the brain, but the tau protein, for example, can reach that. And there is another challenge for medication, too. We have about 100 billion neurons. Two to the power of 100 billion neurons, we have synapses. These

synapses communicate, pass the signals from one neuron to another, by means of neurotransmitters. How many neurotransmitters do we have? About 52.

So, such a small number of neurotransmitters to work for 100 billion neurons and trillions of synapses and medications are going to affect neurotransmitters because we know that, for example, the lack of dopamine causes Parkinson's. We know these things. So, the medication tries to affect that neurotransmitter.

But that neurotransmitter affects so many other parts of the brain too. So, the drugs for nervous system, for brain, by default, is very, very challenging. That's why it is not surprising that the medications for Alzheimer's, the efficacy is very low. For significant effect, the efficacy is about 2.5%. One in 40. For stabilization, they say about 30%. So, the efficacy is pretty low, and that fades away after a while. That's why, in parallel to medication, we have to pay more attention to non-pharmaceutical treatment, on a daily basis because our efficacy seems to be higher than medication efficacy.

MICHAEL: Is there any potential side effects that you've experienced through your treatment?

ZAHRA MOUSSAVI: Our treatment, the current stimulation is pretty safe. There is no lasting side effect so far. We exclude people who have a history of seizures, although we are super cautious. At the amplitude that I'm applying, it doesn't have any effect on the seizure either. Nevertheless, we exclude them. But for people who don't have any implant or any history of seizures, it doesn't really have any lasting side effect. Temporary side effect could be some tingling on the surface, which usually they get used to it. At most, they may get some headache. There is not really any side effect.

MICHAEL: So, just kind of shifting gears a little. What is music, we hear this all time, that music is something that dementia patients respond to positively. What happens with music?

ZAHRA MOUSSAVI: It is being stored somewhere other than speech and our memories. I think amygdala, which is the source of emotions, music has a direct connection to that one somehow because music plays on our emotions. And amygdala is in a part of the brain that is so hard to erase it or change it. That's why the PTSD is so hard to be treated because it is the amygdala that is being affected. With the same token, with the same logic, music affects amygdala.

That's why when you play music that you have experience with, you have emotion with, then all of a sudden, an avalanche of the firework starts to run.

MICHAEL: Right. So, this is stimulation of the brain, the working and the exercising of the brain.

ZAHRA MOUSSAVI: Yes. Use it or lose it. It is very true for the brain too.

MICHAEL: You came to this as an electrical engineer, through a personal experience. But what other kind of “out there” ideas are you curious to explore now?

ZAHRA MOUSSAVI: I would love to understand the mechanism of these non-pharmaceutical treatments a lot better. There are all some theories. I have my own hypothesis too, based on the observations that we have had. But my major question is why some patients respond so well to

gamma band? While some other patients, for example, don't respond to gamma band, they respond better to DC. Why? That's my main, main question. And as I said, I have some hypothesis. But I'm just going by trial and error and finding the optimum treatment for a patient. Why? Because I don't have the means that I wish I could have. I wish I could have the PET scan before and after treatment. That would have given me a lot more indication as this giving some light on why. I wish I had fMRI, that I could do again before and after treatment.

At the moment, all we do is electrovestibulography that has helped to shape some of these hypotheses that we have. For example, I think blood pressure and cerebral vascular symptomology is the key answer, so far, on why some people, for example, do not respond to TMS but respond to electrical stimulation. Or why some people do not respond to higher frequency respond better to low frequency. I think that the answer is in in cerebral vascular symptomology, but which area has that? I don't know. Without a good PET scan, I wouldn't know which area of the brain is most affected by that.

MICHAEL: And how is the medical profession responding? To your treatment, I'm thinking, okay, if I go to a doctor and I'm experiencing, or I know somebody experiencing early signs of dementia, I don't say to them, can you refer me to an electrical engineer? For treatment, right?

ZAHRA MOUSSAVI: 15 years ago, when I started, nobody took me seriously. I was just an engineer. Sure, I'm just an engineer and engineers have problem solving skills. Probably that's the main lesson that I learned from engineering, it's strengthening my problem solving. But nowadays, these are being recognized a lot better. There are a few neurologists in town that do refer patients to me, quite frequently. There are a couple of family physicians who do refer patients as well. And I'm very pleased with that. Mayo Clinic was another one who referred one patient. So now it's better.

MICHAEL: We would think so because there hasn't been good treatment for dementia. You should know that there's a prominent dentist in the city who often says to me, our problems are that we don't have enough engineers working for us because they look at systems. And so, it just struck me that you've moved into this area, but you obviously have deep knowledge, and you're providing a non-pharmaceutical intervention. That's why I asked about the potential side effects, because if there were, you could see how there would be a lot of hesitancy.

So, Zahra, what would someone do if they observe somebody who is, they think, in those early stages of dementia, what would be the next steps? What would you recommend?

ZAHRA MOUSSAVI: Well, I'm sure that most people first go to family doctor and most people are being prescribed with Donepezil. Fine, that is fine. But again, for most people that is not effective. I would love to assess these individuals, and it is as easy as sending me an email and I will assess every single volunteer participant myself. I have a good faith on my own diagnostic tests, and we can enroll them in our treatment program. The earlier, the better. The earlier, the more effective our treatment is.

MICHAEL: Thank you for taking the time to speak with me. Fascinating work that you're doing. And I hope that the positive results you're getting continue to advance and that you continue to help people overcome this disease. Thank you.

ZAHRA MOUSSAVI: Thank you so much for inviting me and having me here.

MUSIC FADES IN

EXTRO

MICHAEL: I hope you enjoyed listening to this conversation. If you want to support life-changing research like Zahra Moussavi's, check out our show notes for how you can get involved. Until then, keep thinking big.