A Conversation with Li-Huei Tsai

INTERVIEWER: GARY STIX

Senior Editor, *Scientific American*

Li-Huei Tsai is the Director of the Picower Institute for Learning and Memory, the Picower Professor of Neuroscience in the Department of Brain and Cognitive Sciences at the Massachusetts Institute of Technology (MIT), and a Senior Associate Member of the Broad Institute.

Gary Stix: Could you talk a little bit about the whole Alzheimer's field, which is a focus of a lot of your work, and the current state of the Alzheimer's field? There are enormous numbers of drugs, but I always hear about 99-point-something that just have failed. There's a real worry in the field that there's no clear directions forward. Your work approaches some of the problems of the biology of Alzheimer's in new ways. Could talk about what you think that problem is?

Dr. Tsai: I think everybody knows about Alzheimer's disease and everybody is afraid of Alzheimer's disease. I've talked to people who said they would rather have cancer than having Alzheimer's disease because in the late stage, people develop dementia and they need full-time care and they don't remember. They forget who they are. They forget their loved ones and their close friends, and they also lose their dignity. Unfortunately, the reality is that the society is aging and Alzheimer's disease is an age-dependent neurodegenerative disease. In the next two to three decades, the number of Alzheimer's patients is likely to double.

Gary Stix: That's about 10 or 11 million people?

Dr. Tsai: Yeah, right now it's about 5.4, 5.5 million people in the US. Worldwide, it's hard to estimate, but probably 45 million people. That's probably an underestimation, actually. A lot of people go undiagnosed.

When it comes to therapeutics, we have a few drugs approved by the FDA [Food and Drug Administration] and they are so-called "symptom-modifying" drugs. They alleviate the symptoms temporarily. They don't really revert the disease. Certainly, not even close to curing the disease. There is a lot of effort in the pharmaceutical industry to come up with better and more effective drugs, but we all know there have been a lot of high-profile failures of late-stage clinical trials.

Gary Stix: A lot of the drugs have focused on amyloid and in some way removing amyloid. There's still some hope for that, but these drugs that go in are antibodies that remove the amyloid. So far, there's been no clear success.

Dr. Tsai: There is the notion that amyloid accumulation in the brain happens very early on in the course of the disease. The notion is that it takes probably a couple of decades for the amyloid to build up. During this period, there is this long time of a so-called asymptomatic stage or presymptomatic stage. The older trials, so far, have been conducted in patients with moderate or even mild to moderate Alzheimer's disease.

Gary Stix: So there's a feeling it might be too late?

Dr. Tsai: They all fail. The feeling right now is that once the patients start to show symptoms, it's probably too late. The effort in the industry, right now, is to identify people who are in the very, very early stage or who don't show very noticeable symptoms yet, to target them.

Gary Stix: But it's still not clear yet whether removing amyloid is going to be useful therapeutically?

Dr. Tsai: In humans, no. Yeah, we don't know.

Gary Stix: You have looked at some new ways of modulating both amyloid and attacking Alzheimer's in other ways, like a noninvasive therapy—no drugs—that might have an effect on amyloid and perhaps some of the other signs of Alzheimer's like the tau protein. Could you talk about that?

Dr. Tsai: When I look at Alzheimer's disease, obviously there have been decades of work. People look at molecules and pathology and abnormal protein aggregation and genes. Today, many genes have been identified to associate with Alzheimer's disease. There are several disease-causing genes and then there are two to three dozen so-called "risk genes" that can increase the risk for people to develop Alzheimer's. We've known a lot about genes and molecules, but when it comes to the brain and how the molecules and genes and proteins interact with the activity of the brain cells, we still don't have much information at all.

The fundamental character of our brain is connectivity. Neurons form trillions of synapses so they can communicate with each other. There are many different forms of

connectivity and population dynamics and how information gets processed so that when we see something, we can all very rapidly process that information; when we hear something, we can process that and then the information gets processed. We take that information from our sensory system, and then we've got to quickly make a decision about what to do. Obviously, Alzheimer's disease patients are very impaired in all of these functions, but we absolutely had no clue how their brain network, their brain circuitry, is affected. It's a very important area for us to look at. Perhaps the etiology and the pathophysiology of the disease involve not just genes and molecules, but probably neuronal activity and circuit dynamics itself.

Gary Stix: You're really interested in circuit dynamics.

Dr. Tsai: Absolutely. I think that's just a very fundamental characteristic of our brain. Our brain, basically, is a computer. It's a circuit board. It's just a very powerful one.

Gary Stix: You've come across a new technology that seems to, on a very simple level, clean out some of those circuits. It's not focused so much on amyloid or tau or anything, but it seems to have an effect on circuit function.

Dr. Tsai: Right. We started to look into the oscillatory neural activity. It's a very fundamental type of brain activity. Our brains can fire oscillations—people call them brain waves, as well—at many different frequencies; for example, low-frequency brainwaves are more active during the sleep state. One of those waves, known as the gamma oscillation, is at kind of an intermediate level. It ranges from about 30 to 80 hertz. It's sort of on the higher-frequency, faster side. The gamma band frequency is historically known to be more active when animals or human subjects are more actively engaged in active tasks, like working memory and navigation. When you need to meet a deadline, your brain is firing gamma oscillations very actively.

Gary Stix: But these are a lot of the deficits that you find in Alzheimer's too, right? Even before people are aware of it sometimes, so that it's subclinical?

Dr. Tsai: Exactly. We found that gamma band frequency oscillation is impaired very early on in the course of Alzheimer's disease. We initially did this in animal models. In the animal models we found oscillation deficits before the animals show any behavioral abnormalities. Another group also showed similar results.

Gary Stix: There's a lot of interest now in epileptic activity. In fact, there is a clinical trial going on with Levetiracetam, but it's different than what you're doing. They're treating low-level seizures. You're actually modulating the...

Dr. Tsai: They are modulating too. They show that fast-spiking interneurons known as the PV [parvalbumin]-positive interneurons, their synaptic function is abnormal in their model. Also, their models show significantly reduced gamma oscillations—40-hertz gamma oscillations—and these animals show an epileptic form of discharges.

So, this is all related. When your gamma oscillations are not functional, it cannot control the spiking of the excitatory neurons. You start to see this disorganized spiking pattern of neurons.

Gary Stix: How did you come up with the idea of using LEDs [light-emitting diodes] to modulate some of this activity? Light can modulate certain epileptic reactions. Did that have anything to do with it?

Dr. Tsai: When I show that this LED light flicker can induce gamma oscillations, people will ask me, "Oh, have you ever watched this episode of a Japanese animation called *Naruto*?" I said, "What are you talking about?" And then they say, "There's this strobe light presented in that episode and a lot of kids, they watch it and then they got an epileptic kind of reaction." And so I said, "Do you know what is the frequency of that strobe light?" And it's like 12 or 14 hertz or something like that. So yes, I think that there are reports of epilepsy induced by a flicker but that's a low-frequency light flicker. Anything above 30 hertz, I haven't heard that this kind of frequency would induce seizure-like activity.

Gary Stix: Why don't you describe how you got to the idea of using LEDs from your basic research to actually applying it in an animal model.

Dr. Tsai: Initially, we were very happy just doing optogenetics because there's wonderful results. Then I presented this data to my colleagues at the Picower Institute and one of my colleagues, Dr. Emery Brown, who is actually a physician...

Gary Stix: He's an anesthesiologist, right?

Dr. Tsai: Yes. He said, "These results are wonderful. But you know optogenetics are not going to be applied to humans, not in the next 10 years. You've got to think of a way to do it noninvasively." So he and his postdoc brainstormed with me and my former graduate students over many meetings. We started to really seriously think about the possibility of sensory stimulation, because there are reports that sensory stimuli can induce gamma oscillations. Back then, we didn't really know whether it's likely to work in a small mouse, because most of those experiments were done in larger mammals. Eventually, it was OK. It required some engineering, some programming and stuff like that. We eventually decided, "Okay, why don't we give it a shot?" I really didn't think it would work. We treated it like a fun thing to do. My student just ordered some LED light strips because we were shopping for the cheapest LED we can find. She got us, for less than \$10, a big bunch of LED light strips and Hannah [Iaccarino], she had some computer science background and she can write some code. We started from there and we really didn't treat it that seriously at all, but then when we saw this entrainment in the visual cortex we realized this is actually probably real.

Gary Stix: Didn't Hannah run in and say, after the animals had been exposed to the LED light, that the amyloid was gone?

Dr. Tsai: Was drastically reduced. I was like, “I don’t know. Do I believe this data?” We were very stressed out for a long time because we don’t know what to believe. It’s just something that you don’t really believe. People will say, “Oh, this is too good to be true.” Let me tell you to what extent we were very skeptical about the result. Not only did Hannah have to go back and repeat it many times, we actually had other people who’d never done this kind of experiment before, other people totally working on different projects, reproduce it.

Gary Stix: Before it was published?

Dr. Tsai: Oh, absolutely. It turns out that’s one of the most robust phenotypes you can measure: reduction of amyloids.

Gary Stix: At this point, you have found a reduction of amyloid in the visual cortex, which makes sense because that’s what’s being stimulated. You’re looking at other areas, right?

Dr. Tsai: We’ve started to look at other areas. Obviously, reduction of amyloid in the visual cortex, in the whole scheme of Alzheimer’s disease, it’s not very meaningful, right?

Gary Stix: You want to see one in the hippocampus?

Dr. Tsai: The visual cortex, the sensory part of the brain, is very important. People don’t give it enough credit.

Gary Stix: But that’s an early sign of Alzheimer’s too: all kinds of sensory problems. Smell, vision, I don’t know about hearing...

Dr. Tsai: Yeah, right now I think there is a potential diagnostic. The amyloid in the retina, people can just directly image rather than using this very sophisticated amyloid PET [positron-emission tomography] imaging.

Gary Stix: The question remains whether it does have an impact on the hippocampus, which is the area that deals with memory.

Dr. Tsai: Absolutely. I think that’s very important.

Gary Stix: This has developed a lot of excitement, even in the public. There are people calling you?

Dr. Tsai: Calling me, e-mailing me. A lot of people say, “I know you still have to do a clinical trial, but my mother cannot wait, so can we just create a homemade device and present it to my mother or my grandfather?” I get a lot of messages from people all over the country and all over the world.

Gary Stix: This has become a big priority for you, finding out what’s really going on and what the potential impact could be in humans. You’re starting to look very slowly at what the reaction might be in humans, right?

Dr. Tsai: At MIT, yes. We started... I wouldn’t call it trial... a human study. We start off with healthy young people, just to see in the healthy state how much gamma entrainment we can get from the LED light exposure. The next step we’re going to do is to do it in aged people who are still cognitively normal. Dr. Brown has established that the robustness of oscillation inversely correlates with brain aging. Just by looking at the strengths of oscillation he can predict how cognitively normal the person is. Even healthy aging will lead to decreased gamma oscillations in the brain. We’re going to see how aged people can be entrained to increase their gamma oscillations. Then based on the data, we hope to be able to further optimize the protocol before we try it on people with Alzheimer’s disease.

Gary Stix: So you’re continuing with the basic research, plus a very early translational stage.

Dr. Tsai: Very early, but I think basic research is the key because the more you understand the mechanism, the more you know how to do it.

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