Josef Parvizi

In an interview with *Neuron*, Josef Parvizi shares his thoughts on the role of neuromodulation, the potential of "electroceuticals" and electrical stimulation for the future of clinical neurosciences, the problem of "cortico-centric myopia," and finding inspiration and excitement in working with talented young students.

Josef Parvizi is a Professor of Neurology and Neurological Sciences at the Stanford University Medical Center. He is a physician scientist taking care of patients with epilepsy and running a research lab in system and cognitive neuroscience. Currently, his lab's mission is to study the functional architecture of the human brain by mapping the causal importance and fast temporal dynamics of activations or deactivations across regions of the brain during cognitive experimental conditions, rest, and sleep. His clinical work is about taking care of patients with medication-resistant seizures by working with surgeons to find and remove the source of seizures in their brain and offer them seizure freedom. For this, his team monitors these patients with intracranial electrodes for days. They record directly from clustered neuronal populations across the human brain to probe the functional correlates of their activity and then electrically perturb their activity to probe their causal importance for human subjective experience and behavior. Dr. Parvizi received his MD at the University of Oslo Medical School in 1995 and received his graduate training at the University of Iowa in Neuroscience in 1999. After 3 years of research in the neuroanatomy of the primate brain, he started his clinical training in Neurology at Mayo Clinic (internship), Harvard (residency), and UCLA (fellowship) before joining Stanford in 2007.

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MD PhD, Professor of Neurology and Neurological Sciences, Stanford University Medical Center

Who were your key early influences?

My Neuroscience training started in 1993 when I was a medical student. I went to Santiago, Chile and spent 10 weeks with Humberto Maturana. The deal was simple: I was going to read his books one by one and bring to him exciting questions. I started with a book he and his student Francisco Varela had written together about the brain as a closed loop system (autopoiesis). Working with Maturana was full of joy and I loved every moment of it.

What do you think are the big questions to be answered next in your field?

People often say the big question in cognitive neuroscience is the question of qualia, binding, and consciousness, but the reality is that we know so little about the brain that almost every question about it is really a very big one.

What do you think are the biggest problems/challenge cognitive neuroscience as a whole is facing today?

Corticocentric myopia. We see the so-called "higher" cognitive functions as the sole product of "higher" cortical structures and consider subcortical structures to be only important for "lower" functions. The relationship between cortical and subcortical structures has been seen in a purely hierarchical manner with the cortex in the tower of control and the subcortical structures in a subserving role. This is in my view so myopic that it has blinded us from seeing human cognition and behavior as the product of the brain as a whole system. Hopefully more research on animals will help us gain a better vision.

Where do you see the strongest potential for progress and new breakthroughs in Neuroscience?

Neuromodulation. I really think the future of clinical neurosciences will be in "electroceuticals." Nowadays, we give X mg of a drug to a patient with a neurological or psychiatric disorder and yet the majority of this drug is deposited in the patient's bones and flesh and doesn't even cross the blood-brain barrier—causing serious bodily ailments. Of those molecules that are stubborn enough to press through the blood-brain barrier, most of them go where they should not go. They go to healthy brain sites and cause more cognitive side effects. Only a tiny fraction of the molecules reach their intended destination. Why can we not implant electrodes in the neural system that is pathological and modulate its function without major side effects and without the patient needing to take pills on a regular basis?

To tackle your favorite research question, is there a tool that either needs to be developed or is currently available that could be implemented in a novel way?

We need to design better tools to modulate the activity of neurons. The field of electrical stimulation is still in its infancy even though it was one of the first tools of Neuroscience. We still do not know how we can entrain neural activity or truly modulate the activity of a set of neural structures. It is true that we can get rid of pathological oscillations in the basal ganglia circuitry in patients with

Parkinson's disease using crude stimulations but that is where the field has stopped. My guess is that we won't be able to offer effective neuromodulation for problems of depression or memory loss or attention deficit until a good paradigm shift happens in the field of brain stimulation.

For this, we need to understand how we can change the activity of a population of neurons with intelligent waveforms beyond simply delivering biphasic square wave pulses with a fixed frequency.

Do you have a favorite anecdote from doing science that you'd like to share (perhaps a key discovery moment)?

One day Jennifer, a medical student working in my lab, knocked on my office door and told me that she is seeing selective activations in the electrodes over a small region of the inferior temporal gyrus when patients are engaged in reading numbers. I was amazed! How can a region of the brain prefer stimuli that are culturally learned? I told her this, "When you think you have discovered something, there is 90% chance that it is an artifact, 9% chance that Luria already reported it, and only 1% chance that it is a novel discovery." I asked her to go and come back with a really convincing case. She spent a year working with the rest of the lab, and together they designed several control experiments and recorded from more patients. At the end, she confidently proved that her original keen observation was totally correct. There is an area within the ventral visual stream that has selective responses to numerals. Later, we have shown that this region selectively works with the parietal cortex in the service of arithmetic functions. Five years later we keep seeing number-selective responses in the same region of the brain, and every time that happens I think of Jennifer knocking on my office door.

How do you find inspiration?

Working with talented postdocs, undergrads, or high school students who think *everything* is possible. I get inspired when I see their eyes shine up when we talk about the brain.

If you could ask an omniscient higher being one scientific question, what would it be and why?

Why did she create a brain with two halves, and why do fibers decussate in the CNS?

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