SPEAKER NOTES

Cognitive and Systems Neuroscience

Summarized by Thomas T. Thomas

Dan Lurie, PhD, is a cognitive and systems neuroscientist. He studies how the brain works and the relationship between the mind and the brain. He's particularly interested in how we control our thoughts and behavior, and why doing so is difficult for some people. To answer these questions, his work uses functional MRI to study brain activity and connectivity in both healthy individuals and people with psychiatric and neurological illness. He also specializes in developing new methods for studying brain structure and function, with the goal of discovering fundamental principles of how neural systems are organized and how they give rise to cognition and behavior.

In his undergraduate work at the University of California, Berkeley, Lurie was research assistant in a lab which focused on understanding the neural basis of psychiatric illness and neurodevelopmental disorders in children and adults. His PhD research focused on understanding how moment-to-moment changes in brain activity are shaped by different aspects of neuroanatomy and connectivity, as well as how these phenomena are disrupted in patients with focal brain lesions due to stroke.

Now a post-doctorate at the University of Pittsburgh School of Medicine, he is focused on extending this work by investigating whether these aspects of brain function can be used to predict individual differences in cognition and behavior, as well as the possibility that they may act as biomarkers for psychiatric and neurological illness. He also has a family member experiencing serious mental illness.

"The brain is all about neurons," Lurie said. These consist of a **cell body** with a long extension called an **axon** to connect it with other neurons. The axon ends in a **synapse** that approaches but does not touch extensions from other neurons called **dendrites.** Information from the neuron travels down the axon and, at the synapse, releases chemicals called **neurotransmitters** that carry the signal to receptors in the next neuron's dendrites.

"The brain has about 86 billion neurons," he said, "and 150 billion synapses—that's more that the stars in our galaxy. The human brain is the most complex thing we know about."

The brain has an outer layer of darker material, the **gray matter,** which is dense with the cell bodies of neurons. Their axons extend into the inner volume of lighter material, the **white matter,** where they connect with different areas of the brain. The surface of the upper part of the brain, the **cerebral cortex,** is folded to accommodate greater surface area inside the confines of the skull, allowing for as much gray matter as possible. "If unfolded, each hemisphere of the cerebral cortex would be about as large as a medium pizza," he said.

There are also darker-appearing, **subcortical** brain structures below the cortex. These include the **amygdala,** which is involved with emotions and decision making, and the **hippocampus,** which is involved with long-term memory and our perceptions of time.

The surface of the cerebral cortex has definite areas associated with movement, the **motor cortex,** controlling the hands, face, feet, and other parts of the body, with the left hemisphere controlling the right side of the body and vice versa. Adjacent to the motor cortex is the **somatic sensory cortex,** which is associated with touch and sensation. So sensation and movement are linked in the brain. There is also an area of **visual cortex** and **auditory cortex** in the cerebral cortex.

"These all constitute the lower-level sensory-motor areas," Lurie said.

There are several ways that neuroscientists study the brain. An older method is called **electroencephalography** (EEG), in which electrodes are placed on the scalp and face to measure the electrical fields produced by the brain. This is useful for sleep monitoring, epilepsy diagnosis and monitoring, and now brain-computer interfacing.

Another means of scanning the brain is **magnetic resonance imaging** (MRI), which uses large magnets to take three-dimensional pictures of the brain's structures, folds, and tissues. **Functional MRI** (fMRI)takes sequential images of the brain and can be used to examine changes in brain activity, represented by changes in blood flow and oxygen levels. Clinical applications of these brain scans include detecting strokes, tumors, and brain injuries as well as diagnosing dementia. And **genetic testing** can indicate risks for Alzheimer's disease, Parkinson's disease, and neurodevelopmental disorders.

"But brain scans cannot diagnose mental illness or predict which treatments will work," Lurie said. "If someone tells you differently, they are trying to sell you something." However, he said, researchers at places like Stanford and the University of California, San Francisco, are studying this. You can track these efforts at the National Institutes of Health's website https://clinicaltrials.gov.

Other resources on brain studies include:

- McGill University's "The Brain from Top to Bottom" (https://thebrain.mcgill.ca).
- Dana Foundation's "Brain Science for a Better Future" (https://www.dana.org) and Brain Awareness (https://www.brainawareness.org).
- Charlie Rose's "The Brain Series" (https://charlierose.com/collections/3).
- Brain and Behavior Research Foundation (https://www.bbrfoundation.org).
- Child Mind Institute (https://childmind.org).

Lurie then opened the meeting to questions.

Q. Would you explain how psychoactive medications work?

A. Selective Serotonin Reuptake Inhibitors (SSRIs) and medications like Ritalin and Adderall work on neurotransmitters at the synapse. Neurotransmitters are held at the synapse and released to the receptors on the adjoining neuron's dendrites. After use, transmitters in the **serotonin system** will be reabsorbed by the synapse, but if there are not enough of these molecules, the signal will be weak. SSRIs keep the excess from being taken back and gives time for the signal to work.

Adderall and Ritalin affect the **dopamine system,** which stabilizes and filters transmission of the neurotransmitter glutamate in the **prefrontal cortex.** This is the part of the brain that modulates higher-order cognitive and executive functions like planning and decision making.

But we don't yet have a clear idea of how these medications go from brain changes to changes in behavior. We only know bits and pieces at the molecular level.

Q. Can you tell by using functional MRI with someone who is hearing voices whether the voices come from outside or inside the brain?

A. Lurie admitted he was not an expert in this area. Hallucinations in the auditory or visual cortex often reflect reverberations in these areas. These may be a form of self-stimulation. When people talk to themselves in their heads, fMRI shows stimulation in the auditory region.

Perhaps, when people hear voices, the brain has become miswired. People with psychosis can't distinguish whether the voices are coming from inside or outside. It would be interesting to contrast the fMRIs of people who hear voices and those who do not, to see if different regions are activated.

Q. Would you talk about the role of GABA [gamma-aminobutyric acid, a primary inhibitory neurotransmitter in the brain] in Tourette's syndrome and autism?

A. Lurie admitted he was not an expert in this area. GABA slows the firing of other neurons, such as when the brain is too active. He "wouldn't be surprised" if GABA had a role in Tourette's.

Q. There is statistical evidence that people with schizophrenia have a death rate from Covid four times higher than others. How would you get research done in this area?

A. Parts of the brain include immune cells that are involved in making sure it stays healthy. Interest in autoimmune diseases in the brain is gaining traction.

Many types of mental illness create increased risk with Covid. But some of this effect may reflect the fact that people with serious mental illness have decreased access to quality health care.

As to getting research started, someone would need to observe the tendency of people getting sick, examine databases to confirm it, then spend a lot of time writing grants to get funding for staff, lab space, equipment, animals for model studies, human subjects for testing, and so on. The National Institutes of Health is the largest funder of neuroscience research, but there is not nearly enough money. A lot of applications get refused, and work that could be done doesn't get done.

Q. Would you talk about the visual cortex and aphantasia [a condition in which people are unable to conjure the image of a scene or face in their minds] or, in my case hypophantasia [reduced ability].

A. We don't know a lot about this. The condition is something that comes out of nowhere.

Q. Would you comment on CBD [Cannabidiol] as an antipsychotic in fMRI studies?

A. Most of the work on marijuana and the brain involves the psychoactive element, Tetrahydrocannabinol (THC), not CBD. There is evidence that THC increases the risk of psychosis, especially among the young who may already have a risk for schizophrenia. There is still stigma about studying cannabis because it is a Schedule 1 drug.

Q. What can you tell us about structural differences in people with autism?

A. Studies have been done on brain volume differences, but they are not reliable. Most studies involve small numbers of people, and for reliable studies you need large numbers—in the thousands—from many sources. But identifying brain differences is the first step in a long way.

More than brain volume, the question is how does brain activity differ? How does brain connectivity differ? And then what are the common things we see across studies?

Q. What are the trends in neuroscience with computers and artificial intelligence (AI)?

A. AI is interesting. These machines are good at finding patterns and making predictions. But we don't always know just what the machine is picking up on to make these calls. Everything depends on the information the system has been trained with. But AI is very good at examining large studies, such as the recent brain scans from 100,000 people in the United Kingdom. It could also have interesting applications on treatments like brain stimulation with electrodes in epilepsy or the effects of dopamine on Parkinson's disease.

However, using AI to model the brain itself is problematic because AI programs are structurally very different from the human brain.

Q. What about popular concepts like some people being "right brained" and others "left brained"?

A. Yes and no. Some lower-level functions are lateralized, like handedness and stimulation of the visual cortex. The left hemisphere may be stronger in language skills while the right hemisphere seems to dominate in attention. But in general, the brain is well connected.

Q. As you get older, what part of the brain starts failing first? The synapses, or everywhere at once?

A. We don't really know. But the best way to keep your brain healthy is with physical and mental exercise—just like keeping your body healthy.