SPEAKER NOTES

What's New in Schizophrenia Research

Summarized by Thomas T. Thomas

A doctor and professor of psychiatry at the University of California at San Francisco, **Sophia Vinogradov, MD,** is an empathetic clinician who has done research at both UCSF and the Veterans Administration Hospital. She is a specialist in clinical neuroscience and its application to brain disorders. She spoke to us on November 28 on the latest research in to schizophrenia, schizo-affective disorder, and related diseases.

SOPHIA VINOGRADOV, MD

"I am becoming increasingly optimistic and convinced of the possibility of recovery and recuperation in terms of symptoms and well-being," Dr. Vinogradov said. She noted that what she would have to say applies to most whole-brain disorders, or those affecting the entire brain and not just a single area or system. She described her work as "translational"—that is, applying her work as a doctor of psychiatry involved with clinical neuroscience to the human condition as a whole. Between the state of the science when she was in medical school and the state of research now, she has seen advances in two key areas.

The first advance is that treatment of schizophrenia and related disorders has moved beyond just treating the troublesome symptoms. These are usually divided into categories like positive—meaning obvious and outward, rather than beneficial—symptoms such as delusions, hallucinations, hearing voices, and paranoia; negative symptoms such as apathy, withdrawal, and inability to feel pleasure (anhedonia); and disorganized symptoms such as being confused and distracted. "We now understand that treatment of these symptoms is not sufficient," she said. "We need to treat them in order to relieve suffering, of course, but to achieve well-being we need to focus on the cognitive symptoms."

There is a huge body of research, she said, to show that in order to achieve wellness, a person with mental illness needs to connect with a community, to be able to function, to work, and to enter into social relationships. The research indicates only a weak correlation between achieving this connectedness and treating the positive and negative symptoms of schizophrenia, while it shows a strong correlation with treating the cognitive symptoms.

Cognition is the function of thinking and processing in the brain. It involves problem solving, planning, learning, and memorizing. These processes are not clearly observed or obvious, but they can usually be inferred when the brain is not processing well. Relatives and friends can tell when a person's thinking processes are "not what they used to be." Cognitive function is related to

outcomes—to success in employment, social engagement, and responses to psycho-social treatments and therapies. While the subtle, underlying symptoms of cognitive dysfunction are not readily observable, they can be tested in a clinical setting.

"There is a huge push by the pharmaceutical companies, the National Institute of Mental Health [NIMH], and the U.S. Food and Drug Administration [FDA] to create a program of research on and development of cognitive enhancing agents," Dr. Vinogradov said. The first step is to establish measures to be used in evaluating a person's cognitive abilities, in order to detect changes in cognition and see if these new agents are working—similar to rating scales in the psychiatric system. The process is well under way, and the doctor said she would expect to see new medications in testing in about three to five years.

"What's remarkable," she said, "is that for the first time the FDA and NIMH are saying that these medications must not only treat symptoms but show improvement in outcomes as well."

Another application of this cognitive focus is in the area of behavioral health, behavioral remediation, or cognitive training—these terms being used interchangeably. "We know the brain is like a muscle," she said. "If you train it in the right way, you can increase its capacity." This effect is called neuroplasticity or cortical plasticity. "The brain is ever changing in relation to what's happening to it. With the correct training, we can improve cognitive processes that weren't strong to begin with by improving the processing pathways."

Dr. Vinogradov has been working in this area for the past six years. She has teamed with Michael Merzenich, PhD, a neuroscientist with the National Academy of Sciences teaching at UCSF. In the past, Merzenich worked with cochlear implants and was involved in The Learning Company in Berkeley, provider of scientifically based educational software, and is now a co-founder of Posit Science in San Francisco, which applies these cognitive functioning principles to older adults.

Together, Drs. Vinogradov and Merzenich have done experiments with animal training and rewards that showed the brain changes physically with learning—that is, it's plastic. Further work with language-based learning in children, especially those with reading problems like dyslexia, led to a package of learning software. Dr. Vinogradov said that the exercises are made interesting and stimulating, like a video game, but they are designed to work on brain pathways that were identified through neurological research.

"So there are two approaches to cognitive improvement—medication and training," she said. "The effect sizes of medication will be modest until you begin exercising the brain. Evolution built our brains to be actively engaged in learning and doing things. In schizophrenia and related disorders, the brain is learning in maladaptive ways during the teenage and early adult years. The plasticity of the brain is set in maladaptive patterns—hallucinations, delusions, apathy—and becomes fixed. A pill alone won't reverse those patterns. But a pill combined with training might."

Studies over the past ten years have shown only modest results for cognitive remediation in treating schizophrenia and related disorders. Dr. Vinogradov believes that is because the practitioners did not have access to current

research in neuroscience, which provides details on the recommended number, intensity, and frequency of the training sessions.

She has just completed the fourth year of a five-year study on cognitive training. The mentally ill subjects were assessed for cognitive function upon joining the study and then assigned intensive training modules for one hour a day, five days a week. Some of the subjects were given actual cognitive training materials, and some received visually interesting materials with no intended training value, as controls. Those getting the treatment showed increases in cognitive processing speed, verbal learning, and verbal retention. Early data from brain imaging with these subjects also showed their brains responding in a way similar to people without a mental illness. Subjectively, people who have taken the treatment say they feel clearer.

"The effect sizes from these training modules are double and triple those of earlier cognitive training and the currently available pharmaceutical agents, because these modules are based on current neuroscience," she said. "If the data continues looking good, we hope to refine the training modules and seek FDA approval of them as a medical device within two to three years.

"Then we'll have a trifecta, because we'll be able to offer patients a combination of pharmaceutical agents to treat the florid symptoms of schizophrenia, cognitive training with software modules to improve their mental processing, and psycho-social therapy to support the person in using his or her newfound skills in a social setting, bringing them back to the community, to employment, and to the family."

Phase II of testing will be to determine whether treatment with these cognitive modules can move out of the laboratory into the settings of home and community treatment centers. Testing with early treatment software in a supported employment program—again with subjects receiving either the actual module or a control—showed that, two years later, 70% those who received the treatment were still employed, while only 5% of those getting the controls were employed.

The second sea change that Dr. Vinogradov identified in treating schizophrenia and related disorders is the movement to early detection and early prevention. "In the last six to seven years we've been working with people in the prodrome," she said. The prodrome is the phase of an illness that comes before its full expression, which is called the syndrome. For example, the prodrome of measles may be a fever, while the syndrome is breaking out in spots. In schizophrenia, the prodrome may include signs and symptoms in adolescents like preoccupation, changes in behavior, failing grades, changes in hygiene, and withdrawal to one's room. These and other factors help to define the "ultra high risk" children, of whom 30% can be expected to go on to the schizophrenic syndrome in two years.

Now we can hope to prevent this progression during the prodrome, she said, through intervention, medication, and support in school in an effort to delay, lessen the severity of, or prevent the first psychotic episode. The UCSF Department of Psychiatry has a Prodrome Assessment Research and Treatment Program (PART), with Dr. Vinogradov as principal investigator, that offers evaluation and treatment for young people at ultra high risk of developing a psychotic disorder, such as schizophrenia. She also noted a program in Portland,

Maine, that undertakes to wipe out schizophrenia by advertising the prodromal signs and symptoms to make parents and professionals more aware of high-risk children, so that they can begin working on intervention.

The prodrome is a time when the person also exhibits cognitive changes, and the hope is that with cognitive training they can be reversed. "We can try to make the brain stronger and healthier and more resistant," she said.

With these opening comments, the doctor invited questions from the audience.

Q. How are young people identified for the PART program?

A. Through community outreach with professionals such as school counselors and pediatricians. Often they may be aware that something is going on and have resources to treat the young person, but the symptoms are not properly diagnosed.

Q. Would cognitive training be useful in cases of dementia?

A. Yes, Posit Science performed a study with approximately 500 participants age 60 and above who were suffering normal cognitive decline with age. They are now applying the results to adults in the early stages of Alzheimer's disease.

Q. Can we improve cognitive function with games and exercises like Scrabble and chess?

A. Not exactly. Cognitive training is a scientifically designed treatment process. However, staying cognitively engaged and stimulated by games and such is good, keeping the level of functioning as high as possible.

Q. Do you see institutions and insurance providers accepting these cognitive medications and treatment, or resisting them? Also, are the pharmaceutical companies aware of the morbid weigh gains associated with some medications?

A. The current antipsychotic medications do a lot for people and their quality of life. But most of them block dopamine—which is good when someone is being actively psychotic. But dopamine is also important in the brain's reward systems, which affect learning and motivation, and in metabolic regulation, which can lead to weight problems. The new class of agents to enhance cognition will work on different brain mechanisms and will not be dopamine blockers.

When the brain engages in plastic changes, it starts to secrete neurotrophins, which are like the brain's fertilizer. When these increase, they can be blocked by metabolic syndromes. So there is a complex relationship between a healthy brain and metabolism and body weight. "Weigh gain is detrimental to brain functioning," Dr. Vinogradov said.

As to acceptance of these new cognitive medications and methods—we don't know yet. "When we discuss them with clinicians," she said, "their faces light up. We don't know if that will translate into Medi-Cal and other services paying for them. But this is real science, the real thing."

Q. Are people with genetic schizophrenia different from those whose disease is without a genetic basis?

A. Schizophrenia is an incredibly heterogeneous disease. Everyone is carrying at least one of the genes involved with schizophrenia. This is part of the human condition, part of an individual's strengths and weaknesses.

Q. How do you approach a subject like cognitive training with a person who has schizophrenia. What do you say and do?

A. You start with basic brain realities—that mental and physical exercise promotes oxygen and plasticity and reduces stress, that medication manages symptoms, and cognitive and social engagement help a person function, learn skills, and have successful experiences.

Q. And where does psychotherapy come in?

A. Psychotherapy is important for support and psycho-social involvement, to help the person engage with the world.