By Rita Baron-Faust

Notes of Emotion and Early Schizophrenia

The emotional nuances of conversation are like notes played on a piano. When we are happy, excited, or angry, the pitch of our voice rises; when we are sad, the pitch falls.

People with schizophrenia cannot hear the emotional tones in a conversation. Daniel C. Javitt, M.D., Ph.D., Professor of Psychiatry, believes emotional tone deafness may be one of the early markers of schizophrenia in adolescents and may provide a window of opportunity for treatments to head off severe symptoms.

Schizophrenia is a chronic and disabling brain disorder associated with three major types of symptoms: positive symptoms, defined as paranoia, auditory and visual hallucinations, and delusions; negative symptoms like lack of emotional expression and comprehension, impaired social interaction, and loss of pleasure in life; and cognitive symptoms such as disorganized thinking, poor concentration, and memory problems. The symptoms typically strike young people in their late teens and 20's, affecting as many as 2 million Americans.

Schizophrenia is now understood to involve both brain chemistry imbalances and functional brain deficits. These deficits, including visual and auditory processing problems, are not unlike those in learning disabilities and autism (once termed "childhood schizophrenia"). But whereas autism and learning disabilities manifest early in childhood, the first signs of schizophrenia emerge in adolescence, says Dr. Javitt, who is also Director of the Program in Cognitive Neuroscience and Schizophrenia at the Nathan Kline Institute for Psychiatric Research (NKI) in Orangeburg, N.Y. During this period, there is a sudden drop in grades (standardized test scores can reflect an IQ decline of as much as 15 points) and difficulties with social interaction, as well as sleep problems and irritability. The premonitory signs preceding full-blown schizophrenia may be misinterpreted as normal adolescent problems, making diagnosis difficult. Dr. Javitt has been working to isolate deficits and to find ways to intervene.

A group headed by Dr. Javitt at the NKI has linked an inability to process vocal tones or musical notes with structural deficits in the primary auditory cortex of the brain. Their research, reported earlier this year in the *American Journal of Psychiatry*, compared tests of vocal emotion identification and music note recognition among 19 patients with schizophrenia and 19 normal controls, correlating the results with magnetic resonance imaging (MRI) of the auditory regions of the brain. Schizophrenia patients not only had trouble distinguishing happy and sad voice inflections but also detecting wrong notes in a common melody. A follow-up study of 24 patients and 17 controls found schizophrenics also could not tell the difference between a question and a statement based on tone of voice.

A specialized MRI technique, called diffusion tensor imaging (DTI), was used to help localize and identify brain deficits. DTI, which tracks water diffusion along nerve cell fibers (axons), found that instead of traveling along the axon to the auditory cortex, some water leaked through the myelin that sheathes the nerve fiber. Myelin acts like electrical insulation to aid signal transmission between brain cells; leakage may impede transmission to the auditory cortex.

"Antipsychotic drugs help balance brain chemistry and alleviate positive symptoms, but are relatively ineffective against negative symptoms and cognitive deficits. These medications work primarily by blocking the neurotransmitter dopamine. Dr. Javitt is working on

a different neurochemical model of schizophrenia, based upon the function of NMDA receptors, which are channels that open in the nerve cell membrane when the cells bind a certain neurotransmitter. These receptors are important for helping the brain form new connections and for regulating the growth of myelin. Deficits in NMDA receptors, therefore, may be behind both the cognitive disturbances and the myelin changes seen with DTI.

The NKI team has identified two amino acids that modulate NMDA receptors that, when given with antipsychotic drugs, also improve negative and cognitive symptoms. "We hope to use those amino acids instead of or in addition to medication to see if they can restore some of the brain function that seems to be breaking down in adolescents," says Dr. Javitt. Candidates for therapy might include teens with a family history of schizophrenia and who have warning signs such as social difficulties and a sharp decline in IQ.

Interventions could also include computer programs to help children with auditory processing learning disorders and to provide social skills training. "It's possible that we could attack this disorder both in terms of learning and modifying brain chemicals to reduce symptoms or prevent it from progressing," says Dr. Javitt. "If we could intervene early enough, we could change the course of schizophrenia." ●

By Peter Sergo

Untangling Alzheimer's

In Alzheimer's disease, neurons in the memory center of the brain become choked by a buildup of two kinds of proteins.

One of the culprits, the tau protein, turns destructive when it becomes prone to forming fibrous tangles. Tau aggregates stifle neurons from inside the cell, where their confinement makes them more difficult to reach than amyloid plaques — another perpetrator in Alzheimer's.

But Einar M. Sigurdsson, Ph.D., Assistant Professor of Psychiatry and Pathology, and his collaborators have found a potentially effective way of combating harmful tau by harnessing the body's immune system. The idea is based on previously published studies and ongoing work to target amyloid beta peptide. In those studies, Dr. Sigurdsson and his collaborators used a vaccine to reduce nerve-damaging amyloid plaques in mice that were susceptible to Alzheimer's. Now, he has employed a different but complementary approach to offset the formation of tau tangles. "The main problem with tau protein is that it's found intracellularly," he says, "so it's difficult to target."

The new study, recently reported in the *Journal of Neuroscience*, used mice that were genetically engineered to produce excessive amounts of tau in the central nervous system. The researchers used a specific piece of the tau protein to immunize the mice, significantly reducing the characteristic loss of motor coordination in them. By producing antibodies that could enter the brain and bind to irregular tau proteins, Dr. Sigurdsson explains, the immune system prevented their aggregation.

By correlating the extent of tau antibody penetration into the brain with preserved motor function, Dr. Sigurdsson confirmed the immune system's potential to combat a major element of Alzheimer's. Now he plans to conduct follow-up studies using mice that slowly develop tangles and cognitive impairments without movement problems.

This finding pushes a potentially effective form of immunotherapy forward by exploring alternatives to other Alzheimer's drugs that broadly impact important brain proteins. "This may have extensive therapeutic implications," says Dr. Sigurdsson. "You specifically target the [problematic] protein." ●

NYU researchers have found a potentially effective way of combating harmful tau protein by harnessing the body's immune system.