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Article

New Roles for the Basal Ganglia in Learning and Memory

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The basal ganglia generate patterns not only for movement, but also for learning and memory, according to Ann Graybiel, PhD, professor of neuroscience at the Massachusetts Institute of Technology.

Improper pattern generation can lead to both drug addiction and levodopa-induced dyskinesias, she said here in a lecture at the AAN Annual Meeting.

At the same time, the basal ganglia are also involved in multiple neuropsychiatric disorders, including Tourette syndrome, autism, depression, and schizophrenia.

The basal ganglia are connected to the neocortex through multiple control loops, "which, as they operate, allow us to select what we'll do," she said. Repeated firing leads to the development of a habit. The system is modulated by reward-related dopamine signals from the substantia nigra.

The connection between motor control and learning circuits in the basal ganglia is most evident in drug addiction. For a cocaine addict, merely observing another person manipulating drug paraphernalia is enough to strongly activate the basal ganglia, as shown by functional MRI studies. The activation is not only in the limbic part, which has been long associated with addiction reward, but also in the motor part, Dr. Graybiel explained.

LESSONS FROM A SIMPLE MAZE

To study these connections further, Dr. Graybiel's laboratory staff places multiple electrodes into the brains of rats or monkeys to examine runs a T-shaped maze, and learns to associate a particular tone with the location of a reward at the end of one arm. They have found that, at first, neurons in the striatum fire throughout the task, but as the rat learns, striatal activity is greatest at the beginning and end, and falls during the middle. "The firing rates of striatal neurons are reprogrammed during learning," she said. "There is wholesale plasticity as we learn."

Drawing on her three decades' of research on the functional anatomy of this central brain region, Dr. Graybiel believes that, together with interconnected cortical areas, the basal ganglia "may act to build higher-order representations of sequential actions and habits."

The basal ganglia are best known to most neurologists for their involvement in movement disorders, including Parkinson disease and Huntington disease. "But as time has gone by, it has become clear there are symptoms beyond the motor symptoms in these disorders, including cognitive and emotional symptoms," she said, indicating the basal ganglia might have a larger sphere of influence.

"How are these different disorders related?" she asked. The answer, she said, is through the overarching function of the basal ganglia as "central pattern generators" for both movements and cognitive processes, "learning and laying down memories that are important in the eventual guidance of our actions."

Figure. New research...

This bimodal pattern is extinguished when the maze no longer holds a reward, suggesting that the basal ganglia are deprogrammed in their behavior over many days. In a standard experiment, a naïve rat response to this new information. In contrast, firing in non-task related areas is inhibited during learning, but reactivated as the learned pattern is extinguished. "This too is a dynamic process, as if somehow the brain can modulate its own signal-to-noise ratio," Dr. Graybiel said.

Investigators have also found that the striatum and hippocampus interact during learning. "These two huge circuits fire in synchrony," linking the fact-based memory of the hippocampus with the procedural memory of the basal ganglia.

NEW GENES THAT REGULATE RESPONSES

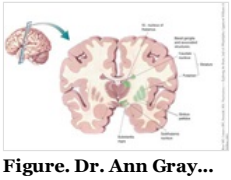

Figure. Dr. Ann Gray...

How do learned habits become the extreme habits characteristic of drug abuse, obsessive-compulsive disorder, or Tourette syndrome? The answers are still being worked out, but Dr. Graybiel's lab has discovered some clues by examining gene activation changes in response to amphetamine.

The effects were largely due to two genes, called *CalDEG-GEF1* and *CalDEG-GEF2*, which influence a central signaling pathway in brain neurons. The two were crucial for development of amphetamine-

"We were stunned to see that after only a single shot of amphetamine, neurons in the basal ganglia have been turned on to express a group of transcription factors," she said. These changes are most prominent in "striosomes," patches of tissue that mediate dopaminergic and possibly cholinergic transmission. Across a range of drugs, the amount of drug-induced stereotypy exhibited by experimental animals correlated to the increase in transcription factor production in striosomes, and the changes were most pronounced in regions implicated in both obsessive-compulsive disorder and drug addiction.

The pieces of this puzzle are still coming together, she indicated. "We are interested in the possibility that the striatum has within it these two genes, and that they are somehow related to dopamine and possibly the

induced stereotypy, and for levodopa-induced dyskinesias.

Dr. Graybiel's work in uncovering the importance of the basal ganglia in learning has been "spectacular," according to Anne Young, MD, PhD, chief of neurology at Massachusetts General Hospital.

cholinergic system as well. The whole process seems to have a 'yin-yang' or 'seesaw' balancing function, in relation to motor output and involuntary movements."

The basal ganglia's role in motor learning has been known for longer, she said, and likely explains the difficulty that patients with Huntington or Parkinson disease have in learning new motor tasks. But the new understanding of the basal ganglia's role in cognitive learning has grown only over the past decade. "More and more data are coming out on this aspect," she said, "changing how we think about these diseases, as well."

ARTICLE IN BRIEF

Drawing from her three decades of research, Ann Graybiel, PhD, discusses the role of the basal ganglia in cognitive and emotional symptoms associated with movement disorders.

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