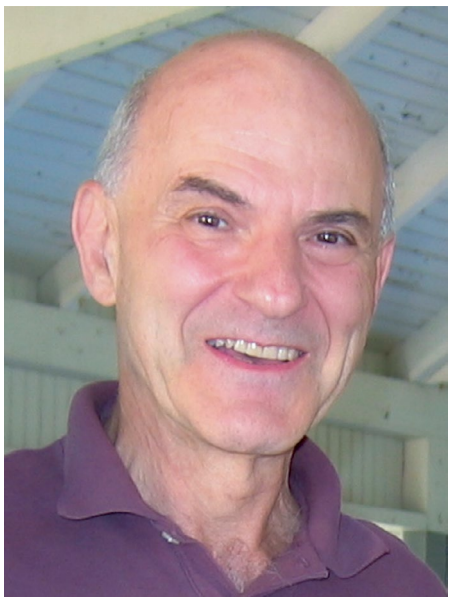
https://doi.org/10.1038/s41593-023-01502-5

George Aghajanian (1932–2023)

By Evelyn K. Lambe

George Aghajanian died on July 4, 2023 in Guildford, Connecticut, at the age of 91. An electrophysiologist and innovator, George was a much-loved mentor, colleague and friend. His laboratory captured the first in vivo recordings of serotonin, norepinephrine and dopamine neurons. For over half a century, George's research at the Yale University School of Medicine opened new fields of discovery in neuroscience.



Back in the 1950s, few medicines existed to treat mental illness, and psychiatry was dominated by the psychoanalytic perspective. George Aghajanian's certainty that mental illnesses were brain disorders marked him as unusual among aspiring psychiatrists of the time. He was fiercely intelligent, with a kind manner and a wry sense of humor. He had family in the business of engineering machine tools and had inherited a talent for tinkering and inventing. But his initial interest in engineering quickly gave way to neuroscience as his curiosity about the brain deepened. Premedical studies at Cornell were followed by medical school at Yale. George's first experiments on the potent psychedelic drug LSD were in the summer of 1957. His mentor was Danny X. Freedman, an early proponent of biological psychiatry and future founder of the American College of Neuropsychopharmacology.

George's independence, resourcefulness and technical aptitude were called into action when his mentor departed for a sabbatical at the National Institutes of Health (NIH), leaving him in charge of the lab and a large quantity of psychedelic drugs. Recounting this time, George smiled about how different the rules were back then. Fascinated by the mechanisms of chemical and organic psychoses, George asked whether LSD and mescaline activated a common brain circuit by examining cross tolerance[1], the ability of one drug to desensitize the effect of another. Identifying their shared, but as-yet undetermined, mechanism of action caught George's imagination and changed the course of his career.

George stayed at Yale for his residency in psychiatry and pursued postdoctoral training in electron microscopy to image neurons. Then the Army's doctor draft, the conscription of doctors into military service, caught up with George in 1962. The Army wanted George, specifically, for his expertise in psychedelic research and training in psychiatry. At Edgewood Arsenal, George worked with a team to assess the cognitive consequences of LSD and test its half-life in human volunteers. During this time, George optimized a blood assay based on the strong natural fluorescence of the psychedelic hallucinogen. In his usual style, George's stories of his Army service emphasized the positive: the people, the science, and amusing anecdotes about golf. Yet this was not an ordinary posting[2]; it was a certain test of George's ethical convictions, courage and diplomatic skill. The following quote, from the memoirs of his senior officer, captures the way George raised important questions and worked toward change within the military hierarchy:

> *Always unassuming, George's profound knowledge of pharmacology and insistence on including rigorous controls in our designs helped raise our standards… Whenever I expressed my beliefs about a pharmacological mechanism, he would listen intently and then sometimes say quietly, "Perhaps not." His mild manner of dissent was disarming. George did not hesitate, however, to back up soft comments with hard scientific facts. He was indisputably correct [when he observed] "Psychopharmacology is not something to dabble in." After 40 years trying to understand drug actions, brain receptors and molecular pharmacology, I realize clearly just how right he was.* (Col. James Ketchum, 2006)[2]

George was relieved to finish his Army service and return to Yale in 1965. He became a founding investigator for a new institute integrating basic and clinical research, the Abraham Ribicoff Research Facilities at the Connecticut Mental Health Center. Psychedelic hallucinogens and their effects on the brain would remain a key direction, but George was quick to center the work in the context of the newly discovered serotonin neurons in the raphe nuclei.

From the time Swedish histochemists characterized serotonin neurons in the brain, George felt compelled to record their electrical activity. His first electrophysiology experiments were conducted at night in 1967, on borrowed equipment, amidst great excitement. His team had already mapped the serotonin system with electron microscopy, then stimulated the raphe nuclei and measured serotonin and its metabolites in the forebrain. Moving next into electrophysiology, with all of its complex equipment, did not intimidate George. But he confided that he was a bit intimidated by John Flynn, the senior colleague whose equipment he borrowed for the initial experiments.

For George, it was not about being first to observe the firing pattern of the serotonin neurons, though that was intriguing. The key aim was to test whether LSD would suppress the activity of these neurons. This was a hypothesis that had been almost a decade in the making, and it proved correct. Serotonin neurons had characteristic rhythmic firing that was silenced by LSD[3]. As George would later discover, this inhibition left the psychedelic hallucinogen free to orchestrate

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its actions through a subset of serotonin's typical receptor targets. It is likely that George left the borrowed equipment in better conditions than he found it. Tinkering was no longer just a hobby but a formidable professional asset. George had now become an electrophysiologist.

Experiments in George's lab were establishing new fields in neuroscience. Subsequent papers contained the first recordings of norepinephrine neurons[4] and dopamine neurons[5]. George and his team did not stop with initial characterization but progressed quickly to determine how these vital neurons responded to relevant psychoactive drugs and medicines. Deeper understanding of important cellular mechanisms, such as autoreceptor regulation, held the key to new therapeutic approaches[6].

The lab attracted a diverse group of energetic, smart people who cared about science and did not back away from challenges. The cutting-edge experiments were the combined efforts of small but formidable teams of mentor and colleagues, for George treated his trainees as colleagues. The intense and interactive nature of electrophysiological experiments required rapid progression. Fortunately, George was an excellent mentor. Over the decades, George trained dozens of scientists who rose to prominence in academia and industry.

Unusually for a scientist at his level, George actively practiced work–life balance and encouraged others to do the same. He openly discussed a number of critical career issues, such as the necessity of saying 'no' to many things in order to focus on personal priorities (for him, his beloved Anne, their family and the lab). George listened carefully and asked insightful questions. These questions, posed at research talks of junior and senior scientists alike, lent him a formidable reputation for identifying key controls or alternative hypotheses. George knew that something worth doing was worth doing well. His generosity with annotated copies of articles became legendary, excitement about science leaping off the pages with each exclamation mark and underlined word.

By the time I joined his lab in 1998, George had fine-tuned his work week to be an optimal balance of the predictable and the new, collegiality and focused scientific pursuits: the biological seminar series on Monday afternoon, his own experiments on Tuesdays and Thursdays, Friday morning Psychiatry Grand Rounds. In between editing, writing and staying on top of the literature, George still had time to brainstorm or to watch in suspense during an experiment to test a new hypothesis. By now, he was more than well aware that the brain would continue to surprise us, but George remained optimistic, calm and methodical. If something could be learned, he studied it. If a gadget would advance a project, he found or invented it. If he was involved in an enterprise, he gently steered it in a constructive direction. He was a remarkable person.

Electrophysiology in vivo and then ex vivo carried George's lab through decades of successful investigations of molecular mechanisms relevant to psychiatry. George's fascination with psychedelic hallucinogens grew stronger over the years, particularly with their enhancement of growth factor and glutamate signaling in prefrontal cortex[7]. Well past typical retirement age, George returned to cellular imaging, using multiphoton microscopy to examine how stress compromises dendrites in prefrontal cortex[8]. His last lab team showed that the rapid-acting antidepressant ketamine could reverse stress-elicited synaptic loss[9] by activating growth factor and glutamate signaling[10]. This discovery was a grand finale for George's lab and presented intriguing parallels between the actions of ketamine and psychedelic hallucinogens.

In February 2020, just before the pandemic shut down the world, I was fortunate to see and talk with George during a celebration of his work at the inaugural George K. Aghajanian Lecture organized by his colleagues at the Ribicoff and the Yale Department of Psychiatry. This event brought together many of George's family and friends from near and far. It was a wonderful opportunity to reminisce with George, to learn more about his life and his own personal highlights, and to appreciate afresh his contributions to the trajectory of neuroscience research.

George's insight, kindness and keen sense of humor are deeply missed.

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Published online: 16 November 2023

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