

Anthony A. Grace: Elucidating the circuitries that underlie schizophrenia and depression may reveal the impact of stress during development and identify novel treatment targets

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After finishing his postdoc at NYU in the Physiology Department under the direction of Rodolfo Llinas, Dr. Grace started as an Assistant Professor of Psychology and Psychiatry at the University of Pittsburgh in the fall of 1985. He was promoted early in the fall of 1991 to Associate Professor of Behavioral Neuroscience and Psychiatry and to Professor of Neuroscience and Psychiatry in July 2003. In September 2010, he was again promoted to Distinguished Professor of Neuroscience and Professor of Psychiatry and Psychology, his current position. He is the Editor-in-Chief of the *International Journal of Neuropsychopharmacology*, the journal of the Collegium Internationale Neuropsychopharmacologicum (CINP, International College of Neuropsychopharmacology). Dr. Grace has offered insights into his personal and professional journey.

Part 1: Anthony Grace – Life and Career

Could you give us a glimpse into your history, emphasizing the pivotal moments that first kindled your passion for science?

When I started my college degree at Allegheny College, I had planned to be premed; however, this was not my passion, and my grades could have been better. However, in the fall of my Sophomore year, I took the course Physiological Psychology and was hooked! I became the lab assistant for the course, teaching rodent surgery to my peers and performing my own experiments. From then on, I made straight As because I had a future for which I was enthused, mainly when I learned I could do this for a living! I did a project for my senior project on the role of dopamine in locomotion, designing and constructing an injection cannula to infuse a GABA agonist into the substantia nigra and measuring rotation. Even though I scored in the 98th percentile in biology and 93rd in psychology in my GREs, after applying to twelve graduate schools I received ten rejections immediately, probably because no one had heard about Allegheny College (a small school with only 1700 students in total). I was accepted to the psychology program at Duke and was on the waiting list in the Pharmacology Department at Yale. It came down to me being at the top of the waiting list and one person to hear from, but as luck would have it, I was accepted! When I arrived, I wanted to work with the scientist who had written a very influential paper that guided my undergraduate project. This was a paper by Walters, Bunney, Roth, and Aghajanian. Coming from a small undergraduate college, I knew nothing about authorship, but I decided to work with the most important person – Judy Walters, the first author! But, of course, she was a postdoc who had left for an independent position, so I went to the second author, Steve Bunney! It turned out that Steve had just finished his residency with George Aghajanian and had started his own lab, so I was his first graduate student and had extensive access to him during my training.



Figure 1. Anthony A. Grace, University of Pittsburgh, USA.

We would like to know more about your career trajectory leading to your most relevant leadership role. What defining moments channeled you toward that leadership responsibility?

When I began in Steve Bunney's lab, I showed early skills for recording from dopamine neurons. I was progressing brilliantly until, all of a sudden, I could not find a single dopamine neuron in my recordings! Unbeknown to me, the postdoc, Lana Skirboll, was performing studies on the effects of chronic haloperidol on the striatum. It turns out that I was accidentally using her treated rats! When I was taking a graduate course from Dr. Gordon Shepherd, I learned about overexcitation-induced depolarization block. This gave me the idea that the dopamine neurons were in a depolarization block due to overexcitation by haloperidol. I found that giving apomorphine, which usually inhibits the neurons, restored activity in the midbrain. This led to my first publication as a first-year graduate student. I had also developed an interest in physiology and setup and was the first to perform *in vivo* intracellular recordings from identified dopamine neurons. I was having fun in the lab, and not knowing what was typically expected of a graduate student, I kept working and publishing, having published 22 papers as a graduate student. My interest in physiology led me to work as a postdoc for Rodolfo Llinas, who is a very talented physiologist and appreciates the philosophical aspects of how the brain works, which I found fascinating. After a short 2½ year postdoctoral





experience and with many publications under my belt, I applied for and was selected as an Assistant Professor at the University of Pittsburgh, where I stayed for my entire career.

Please share with us what initially piqued your interest in your favorite research or professional focus area.

Studying the brain fascinated me from my initial days in college. Taking a physiological psychology course and finding out that the brain had “parts” with functions, I was hooked! This was an intersection between biology and philosophy, which I found fascinating. It was highly unusual for a sophomore to get into this course, as it was a small course with limited enrollment that was usually reserved for Senior psychology majors. But as luck would have it, the professor in the course had a mental breakdown over the summer, and they hired a new faculty member, Ken King. Because he was new, all psychology majors dropped the course, and only 4 remained. This means we all got to work on our own stereotaxics to learn surgery, stimulation, and lesion techniques. Because I did so well, Dr. King chose me to lead the lab for 3 years in college. I read voraciously, and it was my readings about dopamine and schizophrenia that turned me on to studying a system that was responsible for recognizing reality and its disruption in schizophrenia and has been the focus of my research ever since.

What kind of impact have you hoped to achieve in your field by focusing on your specific research topics?

I chose to work in the field of neuropsychopharmacology for two reasons. First, it was trying to understand the most complex puzzle in the universe – how the brain can take in information, process it, and, through this, understand advanced thought processes. However, beyond the intellectual interest, the possibility of helping people suffering from these devastating disorders for which there were not highly effective treatments was also a significant draw. Also, having a love for electronics since grade school, performing electrophysiological recordings was a way to implement my technical background.

Please tell us about your current or most important scholarly focal points within your chosen field of science.

My primary focus is on the biological bases of psychiatric disorders, with an emphasis on schizophrenia and depression, although I have published on OCD and anxiety. The focus is on the circuitry that underlies disorders, their etiology in terms of development and impacts of stress during development, novel treatment targets, and the potential of prevention in susceptible individuals.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you upheld within your research environment?

A saying I heard first from Dr. Ralph Adams, a pioneer in voltammetry, is “the rat is always right.” This is a good mantra to remember when frustrated with experimental outcomes. Indeed, I always tell my students that the results you get that differ from what you expect are the most interesting because they tell you something new about the system. I also let the people working in my lab know that they should contribute to all discussions about our research, that I am not omniscient, and that everyone has a significant contribution. I also believe strongly in trainees “owning” their projects – I do not put them on a segment of a multi-author paper; I prefer that they take ownership of the whole project. I also allow trainees to choose their projects since they are most passionate and productive when working on something that interests them rather than me.

At Genomic Press, we prioritize fostering research endeavors based solely on their inherent merit, uninfluenced by geography or the researchers’ personal or demographic traits. Are there particular cultural facets within the scientific community that warrant transformative scrutiny, or is there a cause within science that deeply stirs your passions?

We need to have better outreach to third-world countries and under-represented minorities. Everyone has unique backgrounds, experiences,

and expertise, and bringing those together into an interactive environment is positive for everyone.

What have you most enjoyed in your capacity as an academic or research leader?

I enjoy interacting with colleagues – some of the best ideas come from conversations over dinner or on the beach rather than at a formal seminar. I find that the best scientists are also the most likable people with whom to interact since they are not always trying to prove they are better. I also very much enjoy what Peter Kalivas has called “Neuroscience Philosophers” – those individuals who think beyond the box and relate their findings to the “big picture” – i.e., what is likely transformative in how we think of the brain.

Outside professional confines, how do you prefer to allocate your leisure moments, or conversely, in what manner would you envision spending these moments given a choice?

There are several things I enjoy. One passion that I developed early on was photography. Indeed, in high school, my two close friends and I worked for a professional photographer and photographed weddings! I also enjoy cooking – this is a stress-free way to express myself. Moreover, I love to travel – to learn about other cultures, histories, and beautiful scenery.

Part 2: Anthony Grace – Selected questions from the Proust Questionnaire¹

What is your idea of perfect happiness?

To be content with my achievements and to share my joy with others. To know I have done my best and lived life to the fullest. And to be recognized as a good person and a good scientist.

What is your greatest fear?

Fear of failure; being able to provide funds for those in my lab to continue their careers and to be able to keep positively contributing to the field. Additionally, I do not want my ego to be out of control: it is essential to remain humble and know that good fortune has helped me a lot.

Which living person do you most admire?

Scientifically, Peter Kalivas has demonstrated the perfect balance of a brilliant and productive scientist, a friendly and supportive person, and someone who focuses on their family. As far as famous people, I think that may be Taylor Swift – not only a brilliant musician but someone who is soulful, kind, and very generous to those around her and the disadvantaged.

What is your greatest extravagance?

I love to cook and also love to travel; the best part of traveling is the ability to form lasting friendships with colleagues from different countries and get the chance to explore new places.

What are you most proud of?

I am very proud of my children and the incredible and thoughtful human beings they have become.

¹In the late nineteenth century, various questionnaires were a popular diversion designed to discover new things about old friends. What is now known as the 35-question Proust Questionnaire became famous after Marcel Proust’s answers to these questions were found and published posthumously. Proust answered the questions twice, at ages 14 and 20. Multiple other historical and contemporary figures have answered the Proust Questionnaire, such as Oscar Wilde, Karl Marx, Arthur Conan Doyle, Stéphane Mallarmé, Paul Cézanne, Martin Boucher, Hugh Jackman, David Bowie, and Zendaya. The Proust Questionnaire is often used to interview celebrities: the idea is that by answering these questions, an individual will reveal his or her true nature. We have condensed the Proust Questionnaire by reducing the number of questions and slightly rewording some. These curated questions provide insights into the individual’s inner world, ranging from notions of happiness and fear to aspirations and inspirations.

**What is your greatest regret?**

Spending more time with my parents while they were still alive.

What is the quality you most admire in people?

Compassion and honesty.

What do you consider the most overrated virtue?

Achieving wealth – especially when it comes at the expense of others.

What is your favorite activity (physical or intellectual)?

I love to walk; it is healthy and gives me time to think and explore. And music – I am very passionate about listening to new music.

Where would you most like to live?

I love living in Pittsburgh – where I grew up, and it is the perfect mix of a small-town attitude with big-city facilities. I also love to be in Italy; it is part of my ancestry, and the people are so lovely, the history incredible, and the food amazing!

What is your most treasured possession?

It is challenging since possessions are such transient things: probably my home, where I raised my kids, and where I feel most safe and comfortable.

When and where were you happiest? And why were you so happy then?

Graduate school was a great time of discovery, personally and professionally, when I grew in so many dimensions.

What is your most marked characteristic?

Being able to talk to anyone and appreciate people for who they are rather than what they have.

Among your talents, which one gives you a competitive edge?

Easy – being passionate about my work and discovering things that can help others in their lives.

What is a personality/characteristic trait you wish you had?

Patience – I have some, but I need to lay back and reflect more.

What do you consider your greatest achievement?

The people who have come through my lab and the success they have had as independent investigators.

What do you most value in your friends?

Honesty and a great sense of humor.

Who are your favorite writers?

I love science fiction, so Isaac Asimov and Frank Herbert.

Who are your heroes of fiction?

I always liked Batman – because of his intellect and compassion for people.

Who are your heroes in real life?

I think that Keanu Reeves is a person I would emulate – he is humble and generous despite being through a rough life.

What aphorism or motto best encapsulates your life philosophy?

I like to trust everyone explicitly until they show me that they cannot be trusted. And be kind to everyone; you do not know what trauma they are carrying.

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