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INNOVATORS & IDEAS: RISING STAR

Daniel H. Wolf: Understanding motivation impairment from clinical, behavioral, and neurobiological perspectives to pave the way for better treatments

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Dr. Daniel Wolf grew up in Los Angeles, completed his BA at Harvard College, MD-PhD at Yale University, psychiatry residency at MGH-McLean, and neuropsychiatry fellowship at UPenn. He is an Associate Professor of Psychiatry at UPenn's Perelman School of Medicine. As head of the Laboratory for Motivation in Psychiatry, Dr. Wolf uses functional neuroimaging to study the neural mechanisms of amotivation and other symptom dimensions in psychosis and at-risk states, aiming to develop novel assessment biomarkers for early-stage drug development. Dr. Wolf also provides outpatient care to individuals with psychosis while supervising clinical trainees. As Director of the Clinical Neurosciences Training Program and Co-Director of the Psychosis T32, he provides seminars and mentoring to medical and graduate students and postdoctoral fellows; he earned the School of Medicine's teaching awards in both Basic Science and Translational Science. He is also an ACNP Fellow and member of the *Neuropsychopharmacology* editorial board. Dr. Wolf answered the Genomic Press Interview, providing our readers with reflections on his life and career.

Part 1: Daniel Wolf – Life and Career

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

As a child, I loved learning about animals from my extensive collection of Jungle Safari Cards, and my mother and father enthusiastically encouraged this passion, along with all other intellectual pursuits (see Figure 2). My father is a clinical and academic neurologist (still practicing and teaching at 90). He would entertain us with medical mysteries at the dinner table, which inspired my lifelong fascination with the brain and the tragedies wrought by its malfunction. The joy and meaning he so obviously found in his work also gave me an implicit belief that one should find a career one truly loved. My first real exposure to scientific research came when I spent a "gap year" after high school and working at USC in the laboratory of Dr. David Galas, a pioneering molecular biologist who passed away last year after an illustrious career spanning academia, government, and industry. Dr. Galas was an inspiring role model – a brilliant physics-trained interdisciplinarian, a lover of literature and philosophy, and an incredibly kind person who populated his group with extremely kind people. In his lab, I poured Petri dishes, and mouth-pipetted E. Coli cultures and typed (twice to catch errors) thousand-base pair DNA sequences into databases. He also handed over to my inadequate direction one of the first PCR projects in the world – I have vivid memories of standing on a bridge between two buildings, carefully pipetting small volumes of DNA templates taken from a refrigerator in one building into a tube containing DNA primer solution taken from another building, to avoid contamination and false positives. The project aimed to identify rare spontaneous DNA mutation hotspots, with the idea that PCR products would only be generated when a deletion event brought the primers close enough together.

Figure 1. Daniel Wolf, MD, PhD, University of Pennsylvania, USA.

I failed to carry his creative strategy to fruition, but other groups published similar efforts in Nature a few years later.

In college, while I flirted with the idea of becoming a translator of Spanish novels, my love for science, coupled with a pragmatic streak, led me to major in biology. My blood-needle phobia suppressed any desire to follow in my father's physician footsteps until I developed a more counter-phobic philosophy late in college. At that point, I decided to pursue combined MD/PhD training. Starting my last year of college and extending into a full year afterward, I worked with Dr. Bruce Schnapp, who was then at Harvard Medical School. Another brilliant and nurturing scientist, Dr. Schnapp, gave me the project of fluorescently labeling Xenopus mRNA so that the mechanisms of intracellular mRNA translocation by motor proteins could be studied in real-time under the microscope. I tackled this effort with gusto and utterly failed to make an mRNA that showed normal translocation (however, helping Charlotte Vines on a different project, I became an expert at running DNA sequencing gels). Although I didn't realize it at the time, being entrusted by Dr. Galas and Dr. Schnapp with

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Figure 2. A young Dan Wolf peering into his father's microscope.

scientific projects that were ambitious, even unattainable, gave me the feeling that I could and should tackle questions that were important even if success was uncertain.

We would like to know more about your career trajectory leading up to your current role. What defining moments channeled you toward this opportunity?

I started the Yale MD-PhD program knowing I was interested in neuroscience, but I needed more specificity, so I met with various potential advisers. As I entered the Connecticut Mental Health Center to meet with Dr. Eric Nestler, there was a sign I can still picture in my mind's eye on the wall outside his lab: "Laboratory of Molecular Psychiatry" – a thrill went through me as I realized that this field I never imagined existed, was in its early days, and I could become part of it. The fact that Dr. Nestler's work in addiction involved understanding the basic mechanisms driving motivation sealed the deal – the idea of helping unravel the mysteries of such a fundamental part of human experience was incredibly compelling. My PhD thesis with Dr. Nestler and Dr. David Russell did not entirely solve the mysteries of motivation, but I did get permanently hooked on trying. I was able to make concrete progress in identifying morphine-induced changes in neurotrophic factor signaling pathway protein levels and activity in the mesolimbic dopamine system and learned a lot of molecular, cellular, and behavioral methods. I also discovered that rats were frustratingly similar to humans in some ways and yet frustratingly dis-similar in others, which later led me to switch my focus to research with humans.

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

In my early clinical exposures to psychiatry, I had fabulous experiences working with individuals with schizophrenia in inpatient and outpatient settings, especially as Chief Resident of the McLean Bipolar and Psychosis program. Dr. Stephan Heckers was the inspirational leader of that program, embodying a synergistic focus on psychopathology and neuroimaging. My neuroimaging work started humbly, manually outlining the hippocampus on many MRI images. Still, it was in his group and with his encouragement that I first developed the idea that hypofunction in brain motivation circuitry likely played a significant role in the pathophysiology of negative symptoms of schizophrenia. My training in addiction neuroscience placed me in the early vanguard of pursuing this idea. Within the addiction field, it was intuitive that hypofunction of subcortical brain reward regions like the ventral striatum should be related to low motivation. However, in the schizophrenia field at the time, the dopamine hypothesis only linked the ventral striatum to hyperfunction and positive symptoms while connecting motivation impairment to hypofunction in the prefrontal cortex. This hypothesized nexus between subcortical dopaminergic brain circuitry, motivation disturbance, and schizophrenia perfectly connected my scientific and clinical interests. My desire to pursue this question led me to Penn and my wonderful mentors Raquel and Ruben Gur, and I have been traveling that path ever since.

What impact do you hope to achieve in your field by focusing on specific research topics?

Motivation impairment is one of the most significant drivers of long-term disability in schizophrenia and in many other neurological and psychiatric disorders as well. I hope that my research will help quantitatively parse heterogeneity in motivation impairment and link particular types or dimensions to specific brain circuits. Then, these assessments can be used in early-stage development of novel treatments and in stratifying participants into such intervention studies. Ultimately, I hope my research will "place a brick" in the wall of science and also have a significant impact on clinical care, alleviating some of the suffering and disability so common in schizophrenia.

Please tell us more about your current scholarly focal points within your chosen field of science?

Methodologically, my strategy involves a boot-strapping triangulation of clinical interviews and self-reports, laboratory behavioral tasks, and functional brain imaging to understand core aspects and heterogeneity of motivation and its impairment. My initial work demonstrated the relationship I expected between ventral striatum hypofunction and global negative symptom severity. I subsequently demonstrated more specific relationships of ventral striatum hypofunction to behavioral motivation using a progressive ratio task I adapted based on rodent addiction methods and then to reward-effort tradeoff decisions in an effort discounting task I adapted from the human delay discounting work of collaborator Joe Kable. Although there remain many details to be worked out and some controversies to be settled in this area, I believe the ventral striatum-amotivation relationship is now one of the most well-established findings in the psychosis functional neuroimaging literature, observed by many groups across many paradigms, not only in schizophrenia but as a transdiagnostic dimension.

I am currently pursuing several different avenues within my broad focus on motivation. One avenue is to further parse motivation impairment in ways that map onto differences in biology and treatment: intrinsic versus extrinsic, approach versus avoidance, and social versus nonsocial. Developing behavioral/fMRI paradigms and self-report measures that capture important domain-specific components and the sizeable domain-general component of motivation has been exciting and challenging. Another focus is on understanding how the same brain circuits can exhibit hypofunction connected to motivation impairment but aberrant hyperfunction connected to paranoia and other positive symptoms. These two major symptom domains often co-occur in the same individuals as part of the schizophrenia and psychosis-risk syndromes, but at least superficially, the proposed abnormalities seem incompatible. In the future, I am especially interested in developing fMRI tasks optimized for within-individual reliability and interpretability for use in small-sample proof of principle pharmacological challenge studies, in developing fMRI methods to examine the interplay of direct and indirect basal ganglia pathways in humans, and in developing approaches to explore how neural plasticity in these

systems contributes to both positive and negative symptoms of psychosis and risk states.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?
One essential habit I developed early on is reading constantly and widely; another is questioning everything; and another is trying to see connections to build a coherent understanding of complex phenomena. Starting in my postdoc and continuing today, the Gurs have provided role models for taking these habits and persistently aiming them towards work that moves steadily towards ultimate clinical application to improve the lives of those with psychotic disorders.

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?
It may sound like a cliche, but finding out the truth is, and should be, the core cause of science. That needs to align with other critical values, but it should not come in second to anything else.

What do you most enjoy in your capacity as an academic or research rising star?
All the free time. But seriously, while I am always busy, my academic career has provided me the flexibility to pursue the things I am most interested in and combine the different roles I enjoy, including research, teaching, and caring for patients.

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?
I read psychiatry and neuroscience articles for fun, so it is hard to tell whether I am at leisure. I also enjoy hanging out with my wife and kids, watching movies (ideally in the movie theater) and good TV shows, reading nonfiction and fiction books, and going out for drinks and dinner.

Part 2: Daniel Wolf – Selected questions from the Proust Questionnaire[1]

What is your idea of perfect happiness?
I don't have one of those.

What is your greatest fear?
Saying/writing something embarrassing in response to an interview question? I do not feel anxious about the things that would be objectively most terrible (for example, nuclear war) although I spend a lot of time trying to learn about systems and policies that might prevent them. I get most anxious about objectively minor things that impact me, particularly in my relationships with others. I was a shy kid, and I haven't entirely outgrown that – I consider myself an introvert who likes other people a lot.

Which living person do you most admire?
It is hard to pick one, but Will MacAskill is a good candidate. He combines intellectual depth and rigor while intentionally prioritizing a successful goal of massive positive real-world impact. He also seems nice, though I only know him via podcasts.

What is your greatest extravagance?
I highlight/underline extravagantly when I read articles… I don't do much in the way of financial extravagance.

What are you most proud of?
My wife and children are awesome, objectively and subjectively, and I get to take a little bit of credit for facilitating that.

What is your greatest regret?
I am not much for regret, and I have been enormously fortunate, so I don't have any major regrets. The biggest one is not spending a significant amount of time living abroad. Maybe someday I will.

What is the quality you most admire in people?
Wisdom.

What is the trait you most dislike in people?
Sociopathy.

What do you consider the most overrated virtue?
Brevity.

What is your favorite occupation (or activity)?
Arguing with friends about philosophy, public policy, or science.

Where would you most like to live?
In the hills of Tuscany.

What is your most treasured possession?
Family photographs and writings.

When and where were you happiest? And why were so happy then?
I don't have an objective answer, but in my memory, it is 4th grade, age 9. I am not sure why, I just liked almost everything about my life then, and didn't have much that I worried about.

What is your current state of mind?
A bit preoccupied, but answering these questions is a welcome opportunity to think about other things.

What is your most marked characteristic?
My snazzy wardrobe? But seriously, probably "thoughtfulness".

Among your talents, which one(s) give(s) you a competitive edge?
Thoughtfulness has mixed effects, but overall I think it has helped me succeed.

What do you consider your greatest achievement?
My family.

If you could change one thing about yourself, what would it be?
I would prefer to be less good-looking; I find that it proves too distracting to others. But seriously, I would probably like to be a bit less risk-averse and a bit less self-deprecating.

What do you most value in your friends?
Love and tolerating my limited skill in staying in close touch.

Who are your favorite writers?
Kurt Vonnegut, Toni Morrison, Vladimir Nabokov …

[1] In 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. In 2003 Proust's handwritten answers were auctioned off for $130,000. Multiple other historical and contemporary figures have answered the Proust Questionnaire, including among others Karl Marx, Oscar Wilde, Arthur Conan Doyle, Fernando Pessoa, Stéphane Mallarmé, Paul Cézanne, Vladimir Nabokov, Kazuo Ishiguro, Catherine Deneuve, Sophia Loren, Gina Lollobrigida, Gloria Steinem, Pelé, Valentino, Yoko Ono, Elton John, Martin Scorsese, Pedro Almodóvar, Richard Branson, Jimmy Carter, David Chang, Spike Lee, Hugh Jackman, 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.

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Who are your heroes of fiction?
The Great Brain, Encyclopedia Brown, the members of the Mad Scientist Club ... for some reason, only childhood fiction heroes come to mind; I have since admired many heroic fictional characters, but none that stand out in my memory like those early ones.

Who are your heroes in real life?
I admire many people I do not know personally, who are brilliant and/or brave and changing the world, but the most impactful heroes in my own life are my parents, and my wife, who sustain love, family, work, and trying to do the right thing, over the long haul.

What aphorism or motto best encapsulates your life philosophy?
Can I have two? Moderation in all things, including moderation. And, The wise learn more from fools than fools from the wise.

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