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Editorial

NeuroChat with Dr. Paul A. Newhouse

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The NeuroChat series continues with Q&A's with our first neuro-focused clinician scientist, Dr. Paul A. Newhouse. Dr. Newhouse holds the Jim Turner Chair in Cognitive Disorders and is Professor of Psychiatry, Pharmacology, and Medicine at Vanderbilt University Medical Center, as well as Director of the Vanderbilt Center for Cognitive Medicine. A major focus of Dr. Newhouse's research deals with central nicotinic mechanisms in degenerative brain disorders, and how nicotinic receptor systems function in normal and disordered cognitive functioning in humans. More recently, Dr. Newhouse conducted a Phase I SAD trial of a novel M_1 PAM developed within the WCNDD. Dr. Newhouse brings a unique translational vision to neuroscience, and I invite you to read the discussion below.

Image courtesy of Paul Newhouse.

Tell us a little about yourself and your career path.

I grew up in a very science-minded home. My father is a retired physicist/engineer, and most of the men that I met growing up were scientists. In fact, for a while when I was a small child, I assumed that everybody was a scientist! I started out in college focusing on insect biology and taxonomy but then decided to go to medical school and I left college early to do that. While in medical school, I got very interested in neuroscience and had a seminal experience when I went to the NIH Clinical Center and spent 3 months working with a great group of clinical neuroscientists who were studying the neurobiological basis of unusual disorders such as Huntington's disease and Tourette's syndrome. This really solidified my interest in exploring the biological underpinnings of neuropsychiatric disorders.

I completed my residency in psychiatry and as part of that spent 6 months in Jim Meyerhoff's laboratory at the Walter Reed Army Institute of Research (WRAIR) trying to show (unsuccessfully) that lithium treatment altered cyclic nucleotide production in response to cholinergic drug challenge. I also conducted my first experimental medicine study, administering intravenous physostigmine and oral lecithin to patients with oral-facial dyskinesia to try to improve their symptoms by cholinergic stimulation. This work solidified my interest in cholinergic mechanisms, and when I returned to NIMH as a fellow (after completing my military obligation), I joined a group under Dennis Murphy studying cholinergic mechanisms in Alzheimer's disease. This was where I really developed my skills in human experimental medicine, becoming comfortable with investigational drug infusions, drug development, cognitive neuroscience, and developed analytical skills.

I later returned to WRAIR to direct studies of the potential for neuropharmacologic amelioration of sleep loss, where I learned a lot about how to manage large groups and complex multimodal human drug-treatment experiments. I then moved to the University of Vermont to establish a research group focusing on cholinergic mechanisms in Alzheimer's disease and cognitive aging. We were successfully able to establish the role of nicotinic cholinergic mechanisms on cognitive operations and developed models to test the effect of nicotinic receptor loss on human cognitive performance. I later became involved with a number of companies in the development of novel nicotinic agonists for human use as potential cognitive enhancers and conducted the first multicenter study of chronic nicotinic cholinergic stimulation for the symptoms of mild cognitive impairment. I also developed strong interest in how age-related sex hormone changes affect cholinergic functioning and developed new pharmacologic models for how to study this in humans. In 2011, I was invited to come to Vanderbilt and establish the Center for Cognitive Medicine where we conduct human-based studies of late life neurocognitive dysfunction and the relationship to biological markers of neurodegenerative disease as well as Phase 1−3 studies of novel compounds for Alzheimer's disease. We also work very closely with basic neuroscientists and pharmacologists on the development of novel cholinergic treatment strategies for cognitive disorders.

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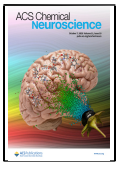

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What are you working on currently?

One of the things that we are most interested in is why women have a higher risk for developing Alzheimer's disease. We believe that part of the answer may be related to change in estradiol support of basal forebrain cholinergic systems at menopause. We are now exploring in a large multicenter study how changes in cholinergic anatomy and functioning after menopause may be affected by early changes in Alzheimer's disease biomarkers in vulnerable individuals. We utilize multimodal approaches including structural and functional MRI imaging, EEG/ERP, novel cholinergic PET radiotracers, fluid biomarkers, and pharmacologic challenge studies with state-of-the-art cognitive assessments. This work will have important implications for drug development and prevention, particularly in individuals who may have enhanced risk for the development of Alzheimer's disease.

What are the major challenges facing early career scientists? How should these challenges be addressed?

I think it is particularly challenging to become a clinical-translational scientist at this time. Whereas the pathway for a PhD basic scientist is perhaps more clearly laid out, for a physician scientist, the competing demands of clinical education and service and the limited opportunities for training in experimental medicine have led to a steep decline in the number of MDs that pursue a clinical/translational research career. This is a tragedy because even the best discoveries in the laboratory have to be tested and translated to patients. Because of this, I think it is critical that basic scientists and pharmacologists connect with human-based researchers to help inform their own work and how these discoveries get translated and how questions get answered in human populations.

What are the major challenges facing neuroscience today? How can these be tackled?

A major issue in my view is the ability to connect findings at the genetic, molecular, or cellular level to how the brain works at a systems level and how that predicts cognitive and behavioral changes or dysfunction. We have a very sophisticated understanding of the molecular underpinnings of neuronal functioning, but that has been difficult to translate into an understanding of how these events work at the level of complex systems. Because there are so many levels of functioning within the central nervous system, a major challenge in neuroscience is to bridge across these multiple levels. This translates into the difficulties we have with our disease models which in general have done an inadequate job of replicating human disorders, in part because animals do not possess the neural circuitry necessary to replicate human cognitive or behavioral pathology. This has subsequently impaired our ability to develop effective therapies.

Human-based researchers have increasingly sophisticated technology to assess the anatomy and workings of the human brain, even in real time. Being able to collaborate with bench scientists to back translate our findings into animal models is going to be critical to establishing adequate modeling so that we can develop effective interventions and to deepen our understanding of the underlying neural circuitry.

What advice would you give to young scientists today?

Science is now a team effort, and the best work is done in teams which have complementary expertise which cuts across levels of analysis and exploration. For example, I am collaborating with pharmacologists, animal behavior experts, and chemists to inform their work in developing novel compounds for cognitive enhancement. Connecting human and basic researchers together in an active way benefits both the quality of the science and the rapidity with which progress can be made. I would encourage young scientists to think of backward and forward translation of their work and connect with people working at levels of systems different from their own. Further, bench scientists should connect with clinical scientists and vice versa. Clinical research works very differently from basic science. The requirements and pace are very different, and the regulatory environment is a whole other world. Rather than simply "throwing things over the fence," it helps to have a foot in both worlds.

What is something about yourself that people would be surprised to know?

I found out a few years ago that I am distantly related to Otto Löewi, who received the Nobel Prize in 1936 for the discovery of the chemical basis of neurotransmission. He called the substance "vagustoff," identified by his co-Nobel laureate Henry Dale as acetylcholine. Another relative for whom I am named was an autonomic physiologist who published many papers on cholinergic neurotransmission in the spinal cord. Thus, there may be a strong "genetic" link to acetylcholine in my family!

Beatles or Stones?

Neither. Brahms or Beethoven for me.

Last book read?

"The Bohemians: The Lovers Who Led Germany's Resistance Against the Nazis" by Norman Ohler

Favorite movie?

That is a tough one. For philosophical questions, I think "Interstellar" was great. For hope amidst tragedy, "Schindler's List."

Lab website address?

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Philosophy or favorite quote?

"There are many examples of old, incorrect theories that stubbornly persisted, sustained only by the prestige of foolish but well-connected scientists. Many of these theories have been killed off only when some decisive experiment exposed their incorrectness. Thus the yeoman work in any science is done by the experimentalist, who must keep the theoreticians honest." Michio Kaku

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