American College of Neuropsychopharmacology
bulletin

Nakul Aggarwal, Ph.D.

J. David Jentsch, Ph.D.

Interview with Nakul Aggarwal, Ph.D.

2024/2025 ACNP-AMP BRAD Fellow

Interviewed by J. David Jentsch, Ph.D.

The ACNP Animal Research Committee, in collaboration with Americans for Medical Progress (AMP), is pleased to announce the selection of Dr. Nakul Aggarwal as the 2024-2025 ACNP/AMP Biomedical Research Awareness Day (BRAD) Fellow. BRAD encompasses a set of ongoing activities intended to educate students and the broader public about the importance of biomedical research, including the humane and responsible study of animal models.

The ACNP Animal Research Committee thanks Paula Clifford and Logan France, DVM from AMP for their ongoing contributions to this program and to the identification of exceptionally qualified fellows, including our past awardees Dr. Stephanie Maddox (2018-2019), Dr. Katie Serafine (2019-2020), Dr. Laura Erwin (2020-2021), Dr. Margaux Kenwood (2021-2022), Dr. Lana Grasser (2022-2023), and Dr. Lindsey Galbo-Thomma (2023-2024).

1. **Can you briefly introduce the topic and main findings from your doctoral dissertation work?**

Childhood anxiety disorders are highly prevalent and constitute a major public health concern, yet current treatments options are limited and often suboptimal for many children. A deeper understanding of the aberrant

neural circuitry underlying anxiety disorders is critical to informing novel, more precise treatments. Disrupted connectivity between regulatory prefrontal regions and limbic structures, including the amygdala, is a core component of the pathophysiology of anxiety disorders. My thesis work focused on leveraging neuroimaging methods (including diffusion tensor imaging and quantitative relaxometry) in young rhesus macaques and preadolescent children with pathological anxiety to investigate how white matter (WM) pathways – bundles of myelinated axons – may be altered in anxiety, particularly those implicated in emotional regulation and prefrontal-limbic communication. Briefly, these cross-species longitudinal studies revealed dynamic, within-individual relationships between anxiety severity and WM – including in the uncinate fasciculus, the major WM tract connecting prefrontal to limbic areas – such that individual increases in anxious behaviors were linked to reductions in WM integrity. Furthermore, a pilot treatment study in nonhuman primates (NHPs) building on these findings provided preliminary evidence suggesting that a pharmacological agent could enhance WM microstructure and attenuate anxiety-related behaviors, indicating that WM may be a potentially modifiable treatment target for novel therapies for pathological anxiety.

2. **Your studies included non-human primates (Rhesus monkeys). For what reasons were the monkey model so crucial to this work?**

NHPs are essential in the study of psychiatric and neurological disorders, particularly in developing a detailed, mechanistic understanding of underlying pathophysiology. With respect to our work in anxiety disorders, NHPs are critical because they can offer highly translational models of pathology, underscored by their remarkable similarity to humans in brain structure, function, and social behaviors. More specifically, anxiety-related behaviors – which at their core are defensive responses to potential threat – are highly evolutionarily conserved. In turn, our NHP model of anxious temperament closely mirrors the behavioral manifestations of maladaptive anxiety in young children. This model allows us to engage in robust translational and reverse-translational studies informed by the observational results in children and investigate brain-behavior relationships in highly controlled experimental settings. Critically, the NHP model enables the invaluable opportunity to perform mechanistic and exploratory treatment studies that are not possible in the clinical setting, allowing us to manipulate specific components of anxiety-related neural circuitry, evaluate causal relationships, and test novel therapeutic strategies that carry direct potential to spur clinical innovation.

3. **As an aspiring MD/PhD, what message would you like to share about the role for animal studies in neuropsychopharmacology research?**

As a translational neuroscientist and aspiring psychiatrist, my ultimate goal is that my research efforts lead to meaningful advances in clinical practice for those suffering from mental illness, a goal that I know I share with many in the neuropsychopharmacology community. Innovation in diagnostic and treatment approaches begins with understanding pathophysiological mechanisms. In psychiatry, where changes in behavior and affect are key manifestations of pathology, animal models of maladaptive behaviors are simply integral to mapping these behavioral constructs onto their neurobiological substrates, which can then serve as candidate biomarkers of disease and novel treatment targets. In summary, animal studies are indispensable in transforming basic science discoveries into better care for our patients.

4. **What would you say to your peers and to ACNP members about the importance of engaging in advocacy for biomedical research, in general, and animal research, in particular?**

Science advocacy is a core responsibility of a career in biomedical research. As most of our research is funded by taxpayer dollars, not only is our work ultimately dependent on public support, but we also maintain an obligation to educate the public and those outside our field and explain the value of our work. This practice also compels us to distill our complex projects to their essence and keeps our research grounded in the patient

experience. Advocacy and education are particularly important in the context of animal research, where mis- and disinformation are more prevalent and can fuel controversy, and it furthermore represents an opportunity for us to highlight for the public the unique translational value and clinical relevance of animal-based biomedical research.

5. **What are your specific advocacy and educational plans, as the new 2024/2025 ACNP-AMP BRAD Fellow?**

My specific advocacy plans for the Fellowship include: 1) stimulating deeper discussion of the importance of animal research among clinicians and researchers across the scientific spectrum, from basic to translational to clinical, to ultimately promote a better understanding of the vital role of animal-based research in advancing healthcare; 2) creating awareness of the role of animal research among patient populations, particularly in relation to commonplace medical treatments that have their origins in animal work, as well as more recent medical breakthroughs based in animal research; and 3) working with ACNP members to emphasize for the broader scientific community the vital role of animal – particularly NHP – research, in neuropsychiatric science, in light of recent notions against it. Very briefly, these efforts will involve initiatives at the 2024 ACNP meeting, efforts to include BRAD-related materials in clinical environments, and drafting a commentary/discussion piece for an academic journal.

From a broader perspective, I am very grateful and excited for the opportunity to serve as the 2024-25 BRAD Fellow, as I complete my medical training and plan to enter a research-track psychiatry residency, with the goal of continuing translational neuroscience research related to childhood mental health.