American College of Neuropsychopharmacology
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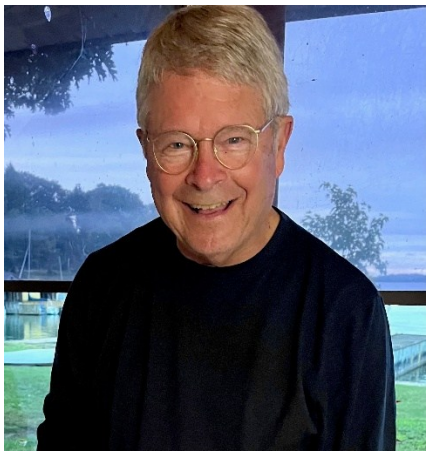

Charles F. Reynolds III, M.D.



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2027 Neuropsychopharmacology Reviews

Panel Session

Making sense of heterogeneity in neuropsychiatric disorders: lifespan pathways to precision and prevention

Chairs: Charles F. Reynolds III, M.D. and Olu Ajilore, M.D., Ph.D.

Panelists: Breno Diniz, M.D., Ph.D.; Eric Lenze, M.D.; Helen Lavretsky, M.D., Ran Barzilay, M.D., Ph.D.

The ACNP panel session for *Neuropsychopharmacology Reviews* will be held on Monday, January 11, 2027, 9:00AM - 11:00AM Pacific Standard Time.

Dealing with brain disorders in older adults is an immersion in complexity—for scientists, clinicians, healthcare system administrators, payors, lawyers, health policy makers, patients, and family caregivers. Complexity is behind our use of the word, "heterogeneity." Neuropsychiatric disorders are notable for their heterogeneity, in which individuals with the same diagnosis can differ in biology, etiology, and treatment outcome. Historically, this heterogeneity has been a limitation to scientific progress in the context of our current diagnostic frameworks. In this symposium, we reframe heterogeneity as signal rather than noise – an opportunity to understand mechanistic pathways, risks, and resilience factors, and

translate these into precision prevention and treatment approaches across the lifespan. Heterogeneity reflects the spectrum from risk to resilience in health trajectories. Resilience is the capacity to adapt, maintain, or regain well-being in the face of adversity—to find meaning and purpose in life despite the multiple challenges that accompany aging. Resilience (or its dearth) occurs not only at the individual level but also in communities.

Emerging from the presentations of the four panelists is the dynamic interplay between geroscience, intervention science, healthy brain aging/resilience, and exposomics (including social determinants of brain aging and wellbeing).

This interplay implies a moral imperative to bridge science and service, that is, to translate what is understood about neuropsychiatric illnesses into practice and policy. The need for discovery and applied science informs the ongoing reconceptualization of DSM by including biopsychosocial markers of the aging brain-- in both health and disease.

Breno Diniz, M.D., Ph.D. will discuss premature aging in serious mental illness (SMIs) and how SMIs, including major depressive disorder, bipolar disorder, and schizophrenia, have long been linked to multiple age-related health outcomes, including cognitive decline, multiple chronic medical conditions, and premature mortality. These factors significantly contribute to the severe disability seen in SMIs, extending beyond the severity of psychopathology. In this presentation, we will present the most recent evidence suggesting that the dysregulation in multiple biological processes related to biological aging can explain the associations between SMI and adverse health outcomes. We will present evidence that accelerated biological aging may be related to treatment refractoriness and identify it as a potential therapeutic target for these conditions.

Eric Lenze, M.D. will address late-life depression as a heterogeneous condition in which treatment response varies widely due to interacting factors such as medical comorbidity, cognitive impairment, frailty, polypharmacy, and underlying neurobiology. An evidence-informed, stepwise treatment algorithm represents a critical advance, providing a structured, pragmatic framework that improves consistency and outcomes in real-world care. At the same time, this approach highlights the limits of one-size-fits-all sequencing and the need to account for individual differences. Building on this foundation, the field is moving toward stratified and precision approaches that integrate clinical phenotyping and emerging biomarkers to better match treatments to patients and reduce variability in response.

Helen Lavretsky, M.D. will review the role of brain health, and risk and resilience factors across the lifespan that can be used for prevention of late-life neuropsychiatric disorders. Brain health represents a dynamic balance of neural, cognitive, and emotional processes that determine resilience to neuropsychiatric illness. In later life, this balance becomes particularly critical as neurobiological and psychosocial stressors converge to shape trajectories of neuropsychiatric and neurodegenerative disorders. We will integrate insights from neuroscience, lifestyle medicine, geroscience, and social determinants of health to emphasize the value of a whole-person, life-course approach. Particular emphasis and opportunities for prevention exist at the interplay between stress physiology, interoceptive regulation, emotional resilience, and cognitive and brain reserve across the aging continuum. Emerging tools and frameworks for brain health and resilience across the lifespan include brain clocks, precision

biomarkers, digital phenotyping, and artificial intelligence, which can be used for risk stratification, early detection, and personalized intervention. By linking resilience mechanisms to measurable biological indices, we argue for the integration of neurobiological, psychological, behavioral, and sociocultural domains to inform next-generation strategies in neuropsychopharmacology, prevention science, and the promotion of healthy brain aging.

Finally, Ran Barzilay, M.D., Ph.D. will explore the exposome as a framework for understanding how accumulated environmental and lifestyle factors across the lifespan shape risk and resilience for mental disorders. It will review key domains of exposure, ranging from early individual-level adversity to neighborhood context, climate, and policy, and how these factors, alongside genetics, influence brain development and trajectories of psychopathology. Clinically, we will consider how integrating exposomic and social determinants data into assessment can refine risk stratification and inform upstream, preventive interventions. For research, the talk will highlight priorities for large-scale, longitudinal exposome measurement and modern causal methods to move from association to mechanism.

This is the second part of NPP's trajectories focus, centered on Trajectories of Mental Health and Illness. Part I was previously published as the 2026 Neuropsychopharmacology Reviews "Trajectories of Mental Health and Illness Across Child and Adolescent Development".

Speakers:

- Breno Diniz, M.D., Ph.D.
    - Washington University in St. Louis
    - Premature Aging in Serious Mental Illness
- Eric Lenze, M.D.
    - Washington University in St. Louis
    - Pharmacotherapy of major depressive disorder in older adults: from an evidence-informed stepwise algorithm to precision medicine
- Helen Lavretsky, M.D.
    - University of California at Los Angeles
    - The role of brain health and resilience in reshaping trajectories of late-life neuropsychiatric disorders
- Ran Barzilay, M.D., Ph.D.
    - Children's Hospital of Philadelphia
    - Exposome and mental health across the lifespan: research and clinical perspectives