Biological Psychiatry

Editorial

Biological Psychiatry: Preserving the Promise

John H. Krystal, Cameron S. Carter, Carrie E. Bearden, and Deanna M. Barch, on behalf of the Editors and Editorial Boards of *Biological Psychiatry, Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, and Biological Psychiatry: Global Open Science*; the Editorial Committee of the Biological Psychiatry family of journals; and the leadership of the Society of Biological Psychiatry

Biological psychiatry is in the midst of a neuroscientific revolution that is transforming our understanding of psychiatric disorders and how they are treated. For scientists to achieve their potential, government, academic institutions, private foundations, and philanthropists (including people with lived experience and their families) must fuel the growth of critical infrastructure, the emergence of illuminating technologies, the vitality of scientific teams, the development of young scientists, and the conduct of research that yields groundbreaking findings. Science is a fragile ecosystem. Even short-term disruptions of any component of this ecology will undermine the infrastructure, teams, and projects. This commentary is intended to acknowledge that the United States has entered an era in which potential threats to the vitality of neuropsychiatric science could delay or deprive its citizens of the fruits of this science, including new diagnostic tests and new treatments.

A Tremendous Opportunity

Why are we so concerned? Psychiatric neuroscience and genomics are just beginning to deliver on their promise to produce fundamental treatment advances that improve the lives of the many individuals in the United States that suffer from the burden of mental illness and substance use disorders. In the past 6 years alone, psychiatric neuroscience has yielded more fundamentally new psychiatric treatments than it has in the preceding 5 decades.

We have experienced a research renaissance, with billions of dollars invested in the development of mechanistically novel treatments for many of the most severe disorders:

- In 2019, the U.S. Food and Drug Administration (FDA) approved esketamine (Spravato), the first mechanistically novel antidepressant in 50 years, the first rapidly acting antidepressant, and currently the most effective FDA-approved pharmacotherapy for life-threatening treatment-resistant depression symptoms. This treatment was discovered at a Department of Veterans Affairs Medical Center affiliated with a university as a consequence of an effort to probe the biology of depression (1).
- In 2019, the FDA approved the first medication for postpartum depression, brexanolone (Zulresso), based on advances in our understanding of childbirth-related hormonal changes on brain function (2), with an oral version, zuranolone (Zurzuvae), approved in 2023. These medications built upon research conducted at American universities and the National Institute of Mental Health Intramural Research Program.
- In 2023, the FDA approved the first disease-modifying treatment for Alzheimer's disease, lecanemab (Leqembi), as the culmination of decades of research conducted at American universities and elsewhere on the role of amyloid protein in the progression of this disorder (3).
- Finally, in 2024, the FDA approved KarXT (Cobenfy) for the treatment of schizophrenia, the first medication since the FDA approval of chlorpromazine in 1957 to treat psychosis without blocking the dopamine D_2 receptor. This drug was discovered in a National Institutes of Health (NIH)–funded study conducted at an American university based on hypotheses about the biology of psychosis and cognitive impairment (4).

This NIH-supported scientific revolution also fueled a new "circuit psychiatry" leading to the FDA approval of transcranial magnetic stimulation treatments for obsessive-compulsive disorder (OCD) and depression and an FDA Humanitarian Device Exemption for deep brain stimulation for OCD. Additional promising new neurostimulation treatments are already working their way through the FDA. Critically, none of the recently approved treatments would have been developed without government support for both fundamental and translational neuroscience research that laid the foundation for these clinical advances.

With this progress already in hand, why do we still need a vital psychiatric neuroscience ecology? Government funding in these areas already lags behind investment in other disease areas. Yet, we predict that if the research ecology remains intact, in the next 10 years, psychiatric neuroscience could harness the power of psychiatric genomics to identify treatments addressing the fundamental causes of psychiatric disorders. Over the past 10 years, psychiatric genomics has accounted for an increasing amount of the risk for developing highly heritable psychiatric disorders, including schizophrenia, bipolar disorder, and autism spectrum disorder (ASD), as well as epilepsy and intellectual disability. In parallel, recent discoveries regarding rare genetic variants (i.e., single gene mutations and copy number variants) have led to promising new genetic treatments (5,6). For example, precision gene editing

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holds great promise for treating syndromic forms of ASD (7), such as mutations in the *SCN2A* gene. In addition, as we have seen for Alzheimer's disease, advances in neuroimaging and other biomarker technologies will yield tests that clinicians will use to guide the treatment of individual patients.

Psychiatric neuroscience holds the potential for scientific breakthroughs that have already been achieved within cancer research. For a growing number of cancers, clinical assessment involves the identification of tumor mutations that predict the response to specific treatments. Cancer treatments also routinely go beyond traditional pharmacotherapy and include antibodies, radiation, and gene/stem cell therapies. For psychiatry, knowledge of the biology and brain circuit dysregulation associated with an individual's illness could similarly guide the selection of medications, antibody treatments, and gene therapies, as well as neurostimulation, psychotherapy, and rehabilitative treatments.

This exciting scientific progress is fueled by a flood of young talent to carry this work into the future. Neuroscience and psychology are among the most popular college majors in the country. Training in psychiatry as a medical subspecialty also has grown in popularity. According to the National Resident Matching Program, over the past 10 years, psychiatry residency applicants increased in frequency from 3.9% (n = 751) to 12.29% (n = 2249) of medical school graduates. The number of neuroscience graduate students also increased substantially (8). The United States has invested significantly in developing these young people, who were at the top of their classes in college, graduate/medical education, and postgraduate training. The talented young investigators who thrive in the current competitive funding environment are the best of the best and they will change the future of mental health evaluation and treatment.

A Fragile Ecology

America has successfully generated the transformative treatment breakthroughs described earlier because of its unique psychiatric research ecology that is heavily dependent upon government support for the infrastructure, people, and processes associated with research. Each of the elements of the fragile U.S. research ecology has been threatened by the executive orders that undercut the NIH and other government research funders, that threaten the vitality and perhaps existence of academic institutions that house and nurture the research, that intrude upon the process of clinical research, and that undermine the initiation and flourishing of research careers. Even a brief interruption of scientific funding at this inflection point in the transformation of mental health science will compromise the current standing and future impact of science in the United States. The creation of a culture of chaos and uncertainty in the academic research ecosystem compounds the impact of actual reductions in funding. It dissuades young scientists from pursuing research careers. It may also dissuade scientists from outside the United States from pursuing training and careers in the United States. It might also create a "brain drain" as talented American scientists may find that other countries are more supportive of their work. Policy changes are already stifling the study of factors such as sex, ancestry, and environmental deprivation that contribute to glaring disparities in health, quality of life, and life expectancy in the United States.

Unless the research climate in this country improves:

- We will lose time as research progress is slowed and perhaps halted in established research laboratories by disruption of federal funding.
- We will lose people as adverse work environments drive people out of research and convince others never to pursue it.
- We will lose breakthroughs because this type of research depends most of all on the convergence of infrastructure, "critical masses" of scientists in teams, and research support.
- We will lose lives as the unchecked burden of mental illness and substance use disorders carry risks including distress, disability, and mortality.

Who Will Suffer?

Every American will suffer. One in 5 Americans lives with a mental illness. Half of American adults say that they have experienced a severe mental health or substance use crisis in their family, according to a CNN/KFF survey (https://www.kff.org/mental-health/report/kff-cnn-mental-health-in-america-survey/). According to this poll, 90% of Americans say that our country is facing a mental health crisis. Everyone in America is affected by the burden of mental illnesses for them, their family members, their friends, and their employees. Mental illnesses are among the leading cause of disability in the United States and they account for approximately 17% of the entire global burden from all medical diseases (https://www.healthdata.org/research-analysis/health-risks-issues/mental-health-our-approach). Psychiatric disorders are medical conditions. Inadequately treated depression shortens life expectancy by up to 10 years (9), while antidepressant treatments such as esketamine reduce all-cause mortality associated with depression (10). Schizophrenia reduces life expectancy by up to 20 years, and treatment reduces some of this risk. In addition, the U.S. economy will suffer, as every dollar the NIH spends returns $2.56 in economic impact (https://www.unitedformedicalresearch.org/wp-content/uploads/2025/03/UMR_NIH-Role-in-Sustaining-US-Economy-FY2024-2025-Update.pdf).

Without progress in psychiatric research, the world's suffering will be compounded. All of the breakthroughs highlighted above began in the United States, with most of them occurring in U.S. universities. America's science is a beacon that inspires progress across the globe. We cannot afford to douse the light.

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