



Testimony
Before the Subcommittee on Domestic
Policy
Committee on Oversight and Government
Reform
United States House of Representatives

Statement for hearing entitled,
“From Molecules to Minds: The Future of
Neuroscience Research and Development”

Statement of
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For Release on Delivery
Expected at 2:00 p.m.
September 29, 2010

Good morning Chairman Kucinich, Ranking Member Jordan, and members of the Subcommittee. I am Thomas R. Insel, M.D., Director of the National Institute of Mental Health (NIMH) at the National Institutes of Health, an agency in the Department of Health and Human Services (HHS). Thank you for this opportunity to present an overview of the current state of neuroscience research at NIMH, with a particular focus on our efforts to address mental disorders affecting U.S. veterans and military personnel, and our efforts to partner with both private industry and other Federal agencies to discover, develop, and pursue new treatments and diagnostic tools for brain disorders affecting all Americans. In my testimony, I will briefly review clinical challenges, treatment options, research opportunities, and some new efforts from NIMH.

NIMH's mission is to transform the understanding and treatment of mental illnesses through basic and clinical research, paving the way for prevention, recovery, and cure. The burden of mental illness is enormous. In a given year, an estimated 13 million American adults (approximately 1 in 17) suffer from a seriously disabling mental illness.^{1,2} According to the World Health Organization, mental disorders are the leading cause of medical disability in the United States and Canada.³ Suicide is the 10th leading cause of death in the United States, accounting for the loss of approximately 34,500 American lives each year, nearly twice the number from homicides.^{4,5} More than half of local jail and state prison inmates suffer from mental disorders, though fewer than half in each population have ever received treatment.⁶ In contrast to many other chronic medical conditions, mental disorders typically begin at an early age, usually before the age of 30. Mental disorders, such as schizophrenia, depression, and

¹ Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of twelve-month DSM-IV disorders in the National Comorbidity Survey Replication (NCS-R). *Archives of General Psychiatry*, 2005 Jun;62(6):617-27.

² U.S. Census Bureau Population Estimates by Demographic Characteristics. Table 2: Annual Estimates of the Population by Selected Age Groups and Sex for the United States: April 1, 2000 to July 1, 2004 (NC-EST2004-02) Source: Population Division, U.S. Census Bureau Release Date: June 9, 2005.

³ The World Health Organization. The global burden of disease: 2004 update, Table A2: Burden of disease in DALYs by cause, sex and income-group in WHO regions, estimates for 2004. Geneva, Switzerland: WHO, 2008.

⁴ Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. Web-based Injury Statistics Query and Reporting System (WISQARS). (www.cdc.gov/ncipc/wisqars)

⁵ United States Department of Justice, Federal Bureau of Investigation. (September 2009). *Crime in the United States, 2008*. (www.fbi.gov/ucr/cius2008/index.html)

⁶ James DJ, Glaze LE. *Bureau of Justice Statistics special report: Mental health problems of prison and jail inmates*. Washington, DC: Office of Justice Programs, U.S. Department of Justice; 2006.

bipolar disorder, are increasingly recognized as the chronic medical illnesses of young people. Overall, 13.1 percent of children ages 8-15 are clinically diagnosable for a mental disorder, though only slightly more than half have received treatment for their disorder.⁷ Mental disorders can be seriously disabling, life-threatening illnesses for which we need reliable diagnostic tests, new treatments, and effective strategies for prevention. Today's treatments are not good enough.

The annual economic costs of mental illness in the United States are staggering. According to the most current estimates, the direct costs of mental health treatment represent 6.2 percent of all health care spending,⁸ which, according to the Centers for Medicare and Medicaid Services (CMS), totals 15.8 percent of the gross domestic product. Indirect costs associated with mental illness, which include all non-treatment-related costs such as lost earnings, Social Security disability payments and homelessness account for even greater expenditures than those associated with direct mental health care. Serious mental illnesses cost the United States at least \$193 billion annually in lost earnings alone.⁹ A conservative estimate places the total direct and indirect annual costs of mental illness at well over \$300 billion.¹⁰

While we have long known that mental disorders are brain disorders, recent research has begun to re-frame these illnesses as disorders of brain development. Between infancy and adulthood dramatic changes are taking place in the brain, not only in size, but also in the structure and function of brain circuits. The behavioral and cognitive symptoms of mental disorders may actually represent late stages of processes gone awry earlier in development. By comparing trajectories of healthy development to those of mental disorders, we can better understand when development moves off course. Redefining these illnesses in terms of developmental trajectories provides unprecedented promise for the prediction and prevention of mental disorders, as well as opportunities to harness this knowledge to improve diagnosis and treatments.

⁷ Merikangas KR, He JP, Brody D, Fisher PW, Bourdon K, Koretz DS. Prevalence and treatment of mental disorders among US children in the 2001-2004 NHANES. *Pediatrics*, 2010 Jan; 125(1): 75-81.

⁸ Mark TL, Levit KR, Coffey RM, McKusick DR, Harwood HJ, King EC, Bouchery E, Genuardi JS, Vandivort-Warren R, Buck JA, Ryan K. *National Expenditures for Mental Health Services and Substance Abuse Treatment, 1993-2003*. SAMHSA Publication No. SMA 07-4227. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2007.

⁹ Kessler, RC, Heeringa S, Lakoma MD, Petukhova M, Rupp AE, Schoenbaum M, Wang PS, Zaslavsky AM. The individual-level and societal-level effects of mental disorders on earnings in the United States: Results from the National Comorbidity Survey Replication. *Am J Psychiatry*. 2008 Jun;165(6):703-11.

¹⁰ Insel TR. Assessing the economic cost of serious mental illness. *Am J Psychiatry*. 2008 Jun;165(6):663-5.

Research = Hope: Fostering Innovations in Diagnosis

One of the greatest challenges in managing mental disorders in the post-genomic era is to “catch up” with the rest of clinical medicine with respect to diagnostic, prognostic, therapeutic, and preventive strategies. Healthcare providers in many specialties are now able to call upon a vast array of clinically relevant biomarkers to accomplish this cardinal task. By contrast, healthcare providers treating mental disorders rely almost exclusively on clinical observation and historical data obtained from patients and other informants. Despite tremendous progress in basic neuroscience, not a single biomarker has been developed with established clinical use in the management of major mental disorders outside the area of substance abuse. To break this logjam, NIMH has funded the study Establishing Moderators/Mediators for a Biosignature of Antidepressant Response in Clinical Care (EMBARC) to identify integrated panels of potential biomarkers (i.e., biosignatures) that are predictive of treatment outcomes in major depressive disorder (MDD). NIMH expects to commit approximately \$12 million to this initiative. In addition, biomarker efforts have been launched for autism spectrum disorder, schizophrenia, and post-traumatic stress disorder (PTSD).

The concept is straightforward. If mental disorders are brain disorders, then biological or subtle cognitive changes might be detected long before the full syndrome becomes manifest with psychosis or a severe mood disturbance. One of the first rules of medicine is the earlier we intervene, the better the outcome. Biomarkers or biosignatures would permit earlier intervention with greater promise of prevention or full recovery, an approach we have called “preemptive medicine.”

Research = Hope: New Treatments

For more than five decades, NIMH has supported high-quality clinical research on the efficacy of psychosocial, somatic, and pharmacological treatments for mental disorders. Randomized clinical trials have helped us identify effective therapeutic interventions for nearly all mental disorders. While we have treatments for all disorders, we do not have treatments for all patients. For too many, current treatments are not sufficient. And for most, current treatments fall far short of a cure. Research with new treatments offers new hope to those with serious mental illness.

PTSD: Researchers today view PTSD as a brain disorder, related to specific circuits in the brain necessary for overcoming or extinguishing fear.¹¹ Recently, scientists have discovered that “fear extinction” in the brain is an active learning process, not a passive process of forgetting.¹² Researchers have identified at least one specific chemical that may help to improve the brain’s process of extinction learning, and it is currently being tested as an adjunct for treating PTSD.¹³ And they have identified periods at which people are most receptive to treatment that may facilitate fear extinction. New research suggests that therapy administered within a certain time frame after the traumatic event may enhance recovery.¹⁴ This research and other studies provide hope that our new understanding of fear extinction can be applied to the development of new behavioral therapies to promote more rapid recovery among those suffering from PTSD.

Schizophrenia: Much of the disability of schizophrenia results from the cognitive deficits, such as memory and attention problems, associated with this complex brain disorder. Current antipsychotic medications do not resolve these cognitive problems. A major effort underway involves development of novel medications and cognitive interventions targeted at this aspect of schizophrenia. In addition to these efforts to develop new interventions to hasten recovery, NIMH recently launched the Recovery After an Initial Schizophrenia Episode (RAISE) project—a clinical trial that will develop and test the coordinated intervention of existing approaches in the early stages of the illness when symptoms may be most responsive to treatment. Importantly, the interventions being tested will be designed from the outset to be readily adopted in real-world health care settings and quickly put into practice.

Mood Disorders: MDD and bipolar disorder (BD) are both characterized by depressive episodes which are long-lasting and difficult to treat. Antidepressants typically take weeks to have an effect, and many patients do not respond adequately to existing medications. Recent studies in patients with either form of mood disorder demonstrate that ketamine can resolve depressed mood within four hours instead of the four weeks required for existing

¹¹ Milad MR, Quirk GJ. Neurons in medial prefrontal cortex signal memory for fear extinction. *Nature*. 2002; 420:70–74.

¹² Bouton ME. Context and behavioral processes in extinction. *Learn Mem*. 2004; 11:485–494.

¹³ Walker DL, Ressler KJ, Lu K-T, Davis M. Facilitation of conditioned fear extinction by systemic administration or intra-amygdala infusions of D-cycloserine as assessed with fear-potentiated startle in rats. *J Neurosci*. 2002; 22:2343–2351.

¹⁴ Schiller D, Monfils MH, Raio CM, Johnson DC, LeDoux JE, Phelps EA. Preventing the return of fear in humans using reconsolidation update mechanisms. *Nature*. 2010 Jan 7;463(7277): 36-37.

antidepressants.¹⁵ The response to ketamine lasts an average of about a week. This work adds to evidence that compounds in the class to which ketamine belongs have potential as rapid and effective medications for depression, including bipolar depression. The potential for side-effects makes ketamine an impractical drug for standard use, but it provides a way to test this approach for developing novel treatments that act more rapidly than existing ones. In short, we are witnessing the beginning of a paradigm shift in how we treat depression and bipolar disorder—from slow and chronic treatment to rapid and acute care.

Advancing Mental Health Research through Collaboration and Partnership

NIMH's mission is not merely to reduce the symptoms and disability associated with mental disorders, but to promote recovery, to extend healthy life, and ultimately, to discover preventive interventions. The success of the Institute's mission depends on the effective collaboration of all stakeholders in the field of mental health. For example, NIMH, the Department of Veterans Affairs (VA), and the Department of Defense (DoD) are committed to research collaborations that will improve the mental health and well-being of military personnel and veterans. Not only is this important to the VA and military, but the knowledge we gain from research collaborations will be critical to the civilian sector: many veterans seek care within their home communities and the problems of soldiers are shared by the society they serve. Moreover, although research conducted on the mental health of military personnel is most immediately applicable in a military context, we expect that the knowledge gained will benefit civilians as well. Although rates of suicide have traditionally been lower for members of the U.S. Army than rates for civilians in the same age range, the rate in the Army began to increase in 2004, doubled by 2008, and reached 160 deaths in 2009 (239 including its Reserve component), exceeding the comparable civilian rate and ranking as the third largest cause of death. For the month of June 2010, the Army reported an astonishing 32 suspected suicides—a record high. Commenting on the high rates of 2009, a recent Army report entitled, *Health Promotion, Risk Reduction, Suicide Prevention*¹⁶ noted, "If we include accidental death which is frequently the result of high risk

¹⁵ Diazgranados, N, et al., A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. *Arch Gen Psychiatry* 2010, 67(8):793-802.

¹⁶ Please see <http://www.army.mil/-news/2010/07/28/42934-army-health-promotion-risk-reduction-and-suicide-prevention-report/index.html?ref=home-headline-link0>

behavior (drinking and driving, drug overdose, etc.), we find that less young men and women die in combat than die by their own hands. Simply stated, we are often more dangerous to ourselves than the enemy.”(p. 11).

In an effort to reduce this increasing rate of suicide among Army personnel, NIMH and the Army have partnered to conduct the Study to Assess Risk and Resilience of Service Members (Army STARRS)—the largest mental health study of military personnel ever undertaken. The study’s goal is to identify, as rapidly as possible, risk and protective factors that will help the Army develop effective strategies for reducing rising suicide rates and addressing associated mental health problems among service members. Army STARRS was officially launched in late 2008 when NIMH and the Army partnered to address the increasing rate of suicide. Over the early months of this effort, both parties realized the need to focus on resilience as well as risk. NIMH and the Army modeled the Army STARRS approach after the Framingham study¹⁷ of cardiac death to conduct a broad investigation of factors leading to adverse outcomes, including suicide, depression, PTSD, and high risk self-destructive behaviors. Accordingly, Army STARRS will have many components, from retrospective studies of completed suicides to prospective studies that will identify the most important predictors of risk and resilience.

In addition to our partnerships with DoD and the VA, we have sought out opportunities to engage other Federal agencies to promote mental health. One such partnership, with HHS’s Substance Abuse and Mental Health Services Administration (SAMHSA), is designed to evaluate suicide hotline training. Crisis hotlines are one of the oldest resources for suicide prevention in the United States. Yet widespread concerns exist about the clinical effectiveness of these services and the extent to which high-risk individuals are using these resources. NIMH is supporting a project to evaluate the effectiveness of a new training program for telephone crisis counselors at suicide hotline centers. The National Suicide Prevention Lifeline (NSPL), the nation’s leading source of immediate help for those dealing with suicide-related issues, funded by SAMHSA, is carrying out the training program across its network of crisis centers. This project is the first controlled study of how trained crisis counselors assess and refer callers,

¹⁷ The Framingham Heart Study is a long-term, ongoing cardiovascular study on residents of the town of Framingham, MA. The study began in 1948 with 5,209 adult subjects from Framingham.

and will provide the first rigorous analysis of the effectiveness of the Applied Suicide Intervention Skills Training (ASIST) gatekeeper program. ASIST involves silent monitoring of calls and follow-up telephone interviews with callers to the hotline, which are used to provide information on the effectiveness of training and the impact of hotline services. In addition, this research will examine the relationships among training for crisis counselors, crisis counselors' performance, and crisis call outcomes. The study findings will provide critically needed data to inform policy decisions and plans regarding the optimization of a network of services for imminently suicidal individuals across the United States.

Conclusion

For the millions of Americans living with mental disorders today, we do not yet have all the answers. Nonetheless, research provides great hope for the future. With the leadership of our colleagues in the military and the VA, there is increasing public recognition that mental disorders are brain disorders: real disorders with real treatments. Genetics and neuroscience are revolutionizing the diagnosis and treatment of mental illness. There has never been a greater need for progress and never a greater opportunity. NIMH is determined to accelerate progress towards prevention, recovery, and cure.

Thank you for this opportunity to present an overview of some of the exciting recent discoveries about the science of mental illness. I look forward to answering your questions.

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Thomas R. Insel, M.D., is Director of the National Institute of Mental Health (NIMH), the component of the National Institutes of Health (NIH) charged with generating the knowledge needed to understand, treat, and prevent mental disorders. Prior to his appointment as Director in 2002, Dr. Insel was Professor of Psychiatry at Emory University. There, he was founding director of the Center for Behavioral Neuroscience, one of the largest science and technology centers funded by the National Science Foundation and, concurrently, director of an NIH-funded Center for Autism Research. From 1994 to 1999, he was Director of the Yerkes Regional Primate Research Center in Atlanta. In addition to these administrative posts, Dr. Insel had a distinguished research career. He was a pioneer in the field of social neuroscience, with classic studies of the neurobiological basis of complex social behaviors in animals. Prior to moving to Emory, Dr. Insel was a scientist in the NIMH intramural program from 1979 to 1994. Early in this period, he conducted clinical research on obsessive-compulsive disorder (OCD), completing some of the first treatment trials for OCD using the selective serotonin reuptake inhibitors (SSRI) class of medications. He has published over 200 scientific articles and four books, including *The Neurobiology of Parental Care* (with Michael Numan) in 2003.

Dr. Insel has served on numerous academic, scientific, and professional committees, including 10 editorial boards. He is a member of the Institute of Medicine, a fellow of the American College of Neuropsychopharmacology, and is a recipient of several awards (A.E. Bennett Award from the Society for Biological Psychiatry, Curt Richter Prize from the International Society of Psychoneuroendocrinology, Outstanding Service Award from the U.S. Public Health Service, and a Distinguished Investigator Award from NARSAD). Dr. Insel graduated from the combined B.A.-M.D. program at Boston University in 1974. He did his internship at Berkshire Medical Center, Pittsfield, Massachusetts, and his residency at the Langley Porter Neuropsychiatric Institute at the University of California, San Francisco.