NIMH Professional Coalition for Research Progress Meeting April 4, 2006

Introduction

The National Institute of Mental Health (NIMH) held its second meeting of the *Coalition for Research Progress* (the Coalition) on Tuesday, April 4, 2006 at the Dana Center in Washington DC. The meeting had two goals: (1) to foster a dialogue between the partners of the Coalition and staff at NIMH and (2) to share a vision of science that represents NIMH's mission and goals.

"Welcome Plenary"

THOMAS R. INSEL, M.D.

NIMH Director, Dr. Thomas Insel, opened the session with a description of the key goals of this meeting: for NIMH stakeholders to hear about current priorities and activities at the Institute and about exciting science in the field. The meeting also provides Dr. Insel and senior NIMH staff with the opportunity to hear directly from stakeholders about any issues of importance to them. Mr. William Safire, Chairman of the Dana Foundation, welcomed the attendees to the Dana Center and expressed his delight that the Coalition was gathered at the Dana Center for this "extraordinarily important" meeting and urged the group to come again next year.

Dr. Insel began his talk describing the burden of mental illness globally and nationally. He noted that there had been no improvement with regard to the burden of mental illness world wide and that mental illnesses account for a greater proportion of years of lost productivity due to disability when compared with other illnesses. He referenced data published in the National Comorbidity Survey that showed that unlike other medical illnesses, mental disorders begin early in life with 50 percent of people experiencing onset of symptoms by age 14 and 75 percent by age 24[1].

Dr. Insel also told participants about a number of scientific advances. He said that there is a "revolution in biology" and that scientists are learning a tremendous amount about the brain and mental illness. First he described the Human Genome Project (http://www.genome.gov/10001772) that gave us a map of the human genome. The Project, completed in 2003, has assisted researchers in learning the function of many genes that were unknown and identifies how one person is genetically different from other people or species. Dr. Insel next described the HapMap Project (http://www.genome.gov/10001688#1): instead of measuring variation in all 3 billion nucleotides that comprise DNA, the HapMap effort measures variation in 300,000 genomic clusters called haplotypes. The cost of genotyping prior to the HapMap was prohibitive. Fortunately, now in the HapMap era, both the cost and the time associated with genotyping have decreased so much that there is now a far greater ability to make significant progress more quickly than in previous years. Dr. Insel highlighted the study of brain systems—an area of research that is being advanced by imaging technology. He told

[1] Kessler RC; Berglund P; Demler O; Jin R; Merikangas KR.; Walters EE. Lifetime Prevalence and Age-of-Onset Distributions of DSM-IV Disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*. Vol 62(6) Jun 2005, 593-602.

participants that with improvements in both spatial and temporal resolution of clinical imaging, the brain is no longer a "black box." Dr. Insel also noted opportunities arising from the completion of four NIMH-funded, large-scale clinical trials (http://www.nimh.nih.gov/studies/index.cfm). These trials represent a significant investment for the Institute over the last six years, and the studies are yielding critical information. These practical, effectiveness trials consist of thousands of patients in real-world settings, who would usually have been excluded from efficacy trials if they had comorbid substance abuse, another comorbid mental illness, or even suicidal ideation.

Dr. Insel provided and update on research funding. He explained that it is critical to set priorities for funding research based on relevance, traction, and innovation. Relevance refers to the pertinence to the NIMH mission; Traction refers to the capacity for rapid progress in research areas where new tools can yield definitive answers to long-standing, relevant questions; and Innovation refers to novel project ideas that may be risky, but hold great promise. In addition, Dr. Insel said it is crucial to preserve training opportunities for the next generation of young investigators. NIH has instituted a new training award, the K99/R00 "Pathway to Independence Award," (http://grants.nih.gov/grants/new_investigators/pathway_independence.htm) designed to help trainees become independent after two years of postdoctoral research. This award will provide up to five years of support in two phases. With regard to innovation, Dr. Insel reminded the Coalition members that NIH's Pioneer Awards (http://nihroadmap.nih.gov/pioneer/index.aspx) are part of the NIH Roadmap and mentioned the NIH High Priority, Short-term Project Award – R56 (http://grants.nih.gov/grants/funding/r56.htm) for grants that are innovative and exciting.

REDUCING FEAR: TRANSLATIONAL RESEARCH ON ANXIETY DISORDERS

KERRY RESSLER, M.D., PH.D., ASSISTANT PROFESSOR, DEPARTMENT OF PSYCHIATRY & BEHAVIORAL SCIENCES, CENTER FOR BEHAVIORAL NEUROSCIENCE, YERKES RESEARCH CENTER, EMORY UNIVERSITY

Dr. Kerry Ressler described his translational research on learning and memory. He noted that multiple parallel memory systems within the brain, ranging from cognitive (implicit and explicit) to sensory to motor to emotional - have all been recognized in recent years and that many psychiatric disorders, particularly those involving fear, can be viewed as disorders of deregulated emotional learning. He told Coalition members that current medications are directed at general symptoms and are often inadequate for targeting specific emotional memory pathways. He said that scientists would like to use enhanced targeted learning to modulate specific memory pathways to study the underlying pathological emotional reactions.

Dr. Ressler explained that post-traumatic stress disorder (PTSD): (1) can occur following exposure to many types of traumatic events—not just war, (2) is highly comorbid with other disorders, (3) creates a level of stress that is a risk for mental illnesses like depression and anxiety disorders, and (4) increases risk for substance dependence, suicide, and homelessness. He likened a panic attack to a fear attack and said that the symptoms for both attacks are the same and occur when the amygdala is activated. Dr. Ressler noted that he is interested in answering the question "what leads to the extinction of fear?" He mentioned that there are many neurotransmitter systems and other brain proteins involved in the extinction of fear: glutamate, the NMDA receptor, brain-derived neurotrophic factor (BDNF), cholecystokinin (CCK), and

anandamide, which is an endogenous cannabinoid. Dr. Ressler's data suggest that the cannabinoid receptor may act primarily on extinction of fear through inhibiting these systems.[2] He also said that more research is needed on BDNF—a protein very important to plasticity, learning, and memory – and PTSD. He also noted "if you could increase the levels of cannabinoids in the brain, perhaps you could enhance the process of extinction." Dr. Ressler briefly mentioned that there is much anecdotal evidence that smoking marijuana makes people with PTSD feel better. However, research has shown that this approach may provide temporary relief, but does not alleviate symptoms over the long term.

Dr. Ressler noted that extinction is often discussed as it relates to drug abuse. He told Coalition members "if you can extinguish the way the cues activate cravings, you might have a significant ability to enhance treatment of drug abuse. It is now known that extinction in drug processing of appetitive cues is also amygdala dependent." He concluded by stating that the association to the amygdala raises the possibility that by understanding the neuronal circuitry, we can develop new therapies in combination with the learning events to enhance functioning of the NMDA receptor, cannabinoid receptor, or CCK receptors – to provide personalized care.

TRANSLATING BETWEEN GENES, BRAIN, AND COGNITION WITH NEUROIMAGING: LESSONS FROM SCHIZOPHRENIA AND WILLIAMS SYNDROME

KAREN BERMAN, M.D.
CHIEF, SECTION ON INTEGRATIVE NEUROIMAGING, CLINICAL BRAIN DISORDERS BRANCH,
DIVISION OF INTRAMURAL RESEARCH PROGRAMS, NIMH

Dr. Karen Berman told Coalition members about her research using neuroimaging to connect genes, brain, and cognition, and studies on schizophrenia and Williams Syndrome. She stated that we do not know what genes are responsible for mental disorders, and while there may be no single gene of major effect, there probably are multiple genes of small effect. She discussed schizophrenia and how her research team used positron emission tomography (PET) to investigate the relationship between two key features of the illness: dysfunction of the prefrontal cortex and dopamine dysregulation. She said that her team demonstrated the hallmark pathophysiology in the dorsolateral prefrontal cortex and that the more abnormal the prefrontal blood flow, the higher the elevation of presynaptic dopamine stores.[3] She also stated that they did not observe this relationship in control subjects. Dr. Berman noted that this was a remarkable finding, because it offered a way to view the co-existence of these two characteristic components of schizophrenia.

Next she discussed what is currently known about genes and schizophrenia and some data about one of the most interesting susceptibility genes that has emerged, Catechol-O-methyl transferase (COMT). She spoke about two forms of the gene – the ancestral valine allele, which is a high activity COMT gene (COMT VA); and a low activity methionine allele COMT gene (COMT MA), which is produced by a human mutation and allows more dopamine to remain in neuronal

[2] Chhatwal JP, Davis M, Maguschak KA, Ressler KJ. Enhancing Cannabinoid Neurotransmission Augments the Extinction of Conditioned Fear. *Neuropsychopharmacology*. 2005 Mar;30(3):516-24.
[3] Meyer-Lindenberg A, Miletich RW, Kohn P, Esposito G, Carson RE, Quarantelli M, Weinberger DR, Berman KF: Reduced Prefrontal Activity Predicts Exaggerated Striatal Dopamine Function in Schizophrenia. *Nat Neurosci*, 5: 267-271, 2002.

synapses. Dr. Berman said that her team of researchers used neuroimaging, in living persons, to find that the COMT VA provides inefficient prefrontal processing of working memory stimuli.[4] She said that researchers are now in a position to rationally construct treatments using genetic information and brain imaging information. She noted that there is a current clinical trial of a COMT inhibitor, *tolcapone*, which is a cognitive enhancer. This is a great example of how scientists can move from patient observations to susceptibility genes like COMT, understand their effects, and move back to the patient to provide treatment.

Dr. Berman also told Coalition members about her research of the behavioral and cognitive deficits of Williams Syndrome. She noted that the goal of her research in this area has been to discover neurogenetic mechanisms that can underlie cognitive deficits and to map individual genes to the brain and the phenotype. Dr. Berman described studies involving very high-functioning Williams Syndrome people with normal IQs, excellent language abilities, relative strengths in many memory domains, and extremely poor visuospatial construction. She said that in normal controls, the amygdala reacts more strongly to faces than scenes. In people with Williams Syndrome, however, the situation is reversed—the amygdala reacts more strongly to scenes than faces. Dr. Berman's team also found that there abnormal regulatory interactions between the prefrontal cortex and amygdala in individuals with Williams Syndrome when compared to controls. She also highlighted the finding that orbitofrontal cortex was not only not differentially activated but also functionally disconnected from amygdala provided evidence for impairment of this regulatory mechanism in Williams Syndrome.[5] Dr. Berman and her team hope to find which genes contribute to the brain phenotypes by studying extremely rare families and looking at knockout mice models. Additional information on Dr. Berman's research can be found at http://www.nimh.nih.gov/press/williamspathway.cfm.

Employer's Guide to Behavioral Health Services

RON FINCH, ED.D., VICE PRESIDENT, NATIONAL BUSINESS GROUP ON HEALTH

Dr. Ron Finch spoke to Coalition members about the concerns of the providers and the payers of health services, specifically those of the large companies who belong to the National Business Group on Health (NBGH). The NBGH, founded in 1974, is the national voice around health care issues for larger employers. The NBGH consists of approximately 245 members, including 62 of the Fortune 100 companies, and NBGH companies provide health care services to over 50 million beneficiaries. Dr. Finch noted that the NBGH examined the President's New Freedom Commission on Mental Health to evaluate how the recommendations would affect employers that provide health insurance and their employees. The examination resulted in a report that Dr. Finch said shows that cost consideration should be given to employers of untreated depressed individuals and that different ways of providing behavioral health services should be reviewed. Dr. Insel said the report has tremendous potential for changing health care in a practical sense. The Employer's Guide can be downloaded with the back-up data from their website at http://www.businessgrouphealth.org/pdfs/fullreport_behavioralhealthservices.pdf.

[4] Meyer-Lindenberg A, Kohn PD, Kolachana B, Kippenhan S, McInerney-Leo A, Nussbaum R, Weinberger DR, Berman KF: Midbrain Dopamine and Prefrontal Function in Humans: Interaction and Modulation by COMT Genotype. *Nat Neurosci*, 8: 594-596, 2005.

[5] Meyer-Lindenberg A, Hariri AR, Munoz KE, Mervis CB, Mattay VS, Morris CA, Berman KF: Neural Correlates of Genetically Abnormal Social Cognition in Williams Syndrome. *Nat Neurosci*, 8: 991-993, 2005.

Dr. Finch next presented data from a survey of larger employers related to direct and indirect medical costs. He singled out sick leave, saying that as a percentage of total payroll, sick leave has almost doubled in two years (a 90 percent increase) while overtime work has increased, and the number of replacement workers has fallen by 33 percent. The survey also included responses from medical directors and benefits managers identifying what was causing the most disability and loss of productivity. Dr. Finch stated that stress was found to be the number one cause. In 2001, the cost of family coverage was a little over $7,000. This year, according to Dr. Finch, costs will rise to $14,545.

Dr. Finch also gave background on the NBGH behavioral health services study. Behavioral health services include services for mental illnesses and substance abuse. Benefit designs have changed rapidly in the healthcare industry. Dr. Finch said that managed care has changed health care significantly, and services have become fragmented in many cases. For example, disability programs often operate separately from the employee assistance programs, and the health plans work separately from the health promotion programs.

After Dr. Finch's presentation, Coalition members provided the following questions, comments, and suggestions:

- Participants suggested that employers require providers to document mental illnesses, including depression, to ensure notation on medical records. Also, employers should offer equal benefits for all care.

- Participants asked if there was a plan to study the changes and impact on expenditures around implementation of the NBGH report. Dr. Insel said that NIMH funded the "Work Outcomes Research and Cost Effectiveness Study" about the cost of depression in the workplace; both absenteeism and presenteeism are included.

- A participant said that previous studies had shown that increased access to mental health care for depression patients with diabetes did not result in a decrease in overall health care costs. Instead, health care costs went up. He asked if there were any data from larger businesses that have increased access to mental health care on their general health care bottom lines. Dr. Finch replied that there were a number of studies, but much is still unknown, particularly concerning how the design of the plans affects adherence with medication.

Discussion &Wrap up

COALITION PARTICIPANTS, NIMH DIRECTOR, AND STAFF

During the course of the meeting, Coalition members had the opportunity to direct questions and comments to Dr. Insel, senior NIMH staff, and presenters about any topic of concern or importance to the stakeholders. Major themes discussed included disparities, basic science, prevention, and social conditions and mental illness.

One participant asked how cultural competence and access for minorities is addressed within NIMH. Dr. Insel said that there are three arms to that very important question. The first is putting a focus on increasing the participation of underserved minorities in NIMH clinical trials.

There are also are a number of trials that are specifically designed for minority groups, as well as epidemiological studies that will be reported later this year. This is a major focus for the NIMH research effort, and staff are now monitoring all NIMH clinical trials to make sure the trials are meeting milestones for diversity. The second arm is making sure that people who care about the issues of minority groups and who come from minority communities are trained in research, so that they can help to lead that effort. NIMH has a number of minority research training programs. Finally, the third arm is to make sure that the NIMH workforce reflects all populations; Dr. Insel said he thinks the Institute could do better in this very important priority area.

Dr. Insel spoke briefly about the issue of funding for basic research, because there is a perception that NIMH no longer funds basic behavioral science. He said that within basic behavioral science, especially basic cognitive science, a series of outstanding applications has been funded in the last year. NIMH will continue to support the best basic science across the spectrum—from behavior and cognition to molecular and cellular studies of brain function.

When asked about prevention of mental illness, Dr. Insel replied that the Institute has a history of supporting research on primary prevention. NIMH is funding research to determine how to predict, preemptively treat, and prevent mental disorders. For example, schizophrenia typically begins in late adolescence. However, screening and early intervention before disease onset might reduce patients' symptoms and functional disability. Early indicators of schizophrenia in teenagers could be sleep disruption, dropping grades, and increased isolation. In the future, individuals with these indicators could be screened for genetic variations that indicate risk for schizophrenia; and people could begin treatment more quickly.

Dr. Insel was asked if NIMH gave emphasis to research on social conditions that lead to mental illness and how social conditions interact with genetic vulnerabilities and the dynamics of normal development. Dr. Insel responded that there is much in the literature about the interaction of genes and environmental factors. He said that the greatest traction is probably in animal work, which is helping to demonstrate that, whether in mice or rats or monkeys, early experience can confer some very long-term changes on how genes are expressed and how neural systems and brains develop.

He also reminded participants that the greatest mental health challenge in America is outside of the mental health system. People are not coming to mental health specialty settings to get care. Instead, mental health care is often given in nursing homes, schools, community centers, primary care settings, and the criminal justice system. Dr. Insel said that the NIMH services research agenda is trying to find a way to match up how we do research with the people in need – this includes a plan to expand research in the criminal justice system. He said that NIMH also must make an effort to expand research in nursing homes.

Dr. Insel concluded by reiterating that he values these meetings because feedback from NIMH stakeholders is essential. He assured attendees that it is important to him that they be well informed about what NIMH is doing, and that they have ample opportunity to participate and express their views. He assured them that "…we are available throughout the year. Many of you do talk to us on a regular basis, and I want to make sure that you understand that this is not a once a year event. We need you as partners. We need input from your communities. We share

the same goals. We all have the same general mission, but we accomplish it in different ways. Thank you very much for spending the day talking to us."

Photographs

Speakers: Dr. Berman, Dr. Ressler, & Dr. Insel


Dr. Insel and Dr. Saffire


Coalition members


Coalition members


Dr. Ron Finch