

Director's Report to the National Advisory Mental Health Council

May 11, 2007

I am pleased to welcome members of the National Advisory Mental Health Council (NAMHC) and other participants and guests to our 215th Council meeting. Since our last meeting in January, the National Institute of Mental Health (NIMH) has made progress in several important areas, which I share with you in this report.

DHHS Update

Mental Illness and Violence

Following the tragic shootings at Virginia Tech in April, the President asked the Secretary of Health and Human Services (HHS), the Secretary of Education, and the Attorney General to visit several states to identify concerns and best practices related to violence in schools, both K–12 and post-secondary institutions. The Director of NIMH and the Administrator of the Substance Abuse and Mental Health Services Administration (SAMHSA) were asked to accompany the Secretary of HHS on this “listening tour.” Each state had a history of a mass shooting, often involving schools and sometimes related to mental illness. From April 26-30, the team visited with governors, their experts in mental illness, education, and law enforcement, and families in West Virginia, Minnesota, Utah, Colorado, Tennessee, Florida, and Texas. The President has asked for a report of findings before the end of May 2007. According to Secretary Leavitt, this report will not focus on Virginia Tech specifically, but will identify short-term and longer-term issues that can frame a national discussion about youth violence. From the NIMH perspective, we expect this discussion to clarify that (a) mental illness is not involved in most acts of violence, (b) violence by those with mental illness usually occurs in those who are not treated and is most often self-directed (e.g. suicide), and (c) recent acts of violence by those with mental illness, while rare, remind us of the need to provide better access to treatments for students both in K–12 and post-secondary education.

Combating Autism Act

The Combating Autism Act was signed by the President on December 19, 2006. This new law assigns the Secretary of HHS responsibility for implementing several new authorities in research and services for those with autism spectrum disorders. Among the provisions is a new Interagency Autism Coordinating Committee (IACC) which will include several Institutes of the National Institutes of Health (NIH), the Center for Disease Control and Prevention (CDC), SAMHSA, Department of Education, and at least six public members, including one diagnosed with autism spectrum disorder. This Committee will coordinate autism research across the Federal government and private sector. The Act requests the Committee oversee a Strategic Plan for autism research. The Office of the Secretary and Office of the Director at NIH are in the process of delegating the authority for implementing the IACC and the Strategic Plan to NIMH.

NIH-Wide Update

NIH Roadmap – Selected Updates

The NIH Roadmap is a trans-NIH effort to support innovative science, stimulate interdisciplinary research, and reshape clinical research to accelerate medical discovery and improve public health. Currently, workgroups co-chaired by the Directors of NIH Institutes and Centers (ICs) and populated by nominees from interested Institutes are developing initiatives for “Roadmap 1.5.” The five initiatives under development for consideration by NIH leadership are listed below. A full summary of Roadmap activities can be found at <http://www.nihroadmap.nih.gov/>.

- *Microbiome* – The Microbiome is the full collection of microbes (bacteria, fungi, viruses, etc.) that naturally exist within the human body. Initiatives in this area would focus on developing a deeper understanding of these communities of microbes in order to determine how they affect human health.
- *Protein Capture/Proteome Tools* – The Proteome is the complete set of proteins in the body. Efforts in this area would support developing and making available to the scientific community high quality probes specific to every protein in humans and some animal models. This would foster the ability to characterize protein function in health and disease and to monitor the markers of a disease in order to refine early prevention efforts and to identify potential therapeutic targets.
- *Phenotyping Services and Tools* – A human phenotype is the total physical appearance and constitution of a person, often determined by multiple genes and influenced by environmental interactions. Initiatives in this area would encourage the development of resources to systematically catalog human phenotypes in an effort to characterize complex diseases and disorders.
- *Inflammation as a Common Mechanism of Disease* – The goal of this initiative is to uncover as-yet-unknown immune mechanisms and mediators of inflammation as well as genetic factors, environmental triggers, and the relationship of inflammation to disease.
- *Epigenetics* – Epigenetics is the study of stable genetic modifications that result in changes in gene expression and function without a corresponding alteration in DNA sequence. Epigenetic changes have been associated with disease, but further progress requires the development of better methods to detect the modifications and a clearer understanding of factors that drive these changes.

Ongoing NIH Roadmap Initiatives

Pathways to Discovery: Molecular Libraries and Imaging Roadmap

The December 2006 mid-course review of the NIH Molecular Libraries and Imaging Roadmap initiative (MLI) led to approval for extending a five-year formal funding phase of the Molecular Libraries Screening Centers Network (MLSCN). This funding phase will be named the Molecular Libraries Probe Production Centers Network (MLPCN) with the aim of supporting a nationwide network to implement HTS and chemical probe development in a comprehensive and effective way.

Institutional Clinical and Translational Science Award

The ever increasing complexities involved in conducting clinical research are making it more difficult to translate new knowledge to the clinic, and back again to the bench. These challenges limit professional interest in the field and hamper the clinical research enterprise at a time when it should be expanding. The purpose of this Roadmap initiative is to assist institutions in creating an academic home for clinical and translational science that has the resources to advance a cadre of well-trained multi-disciplinary investigators with access to innovative research tools and information technologies to promote the application of new knowledge and techniques to patient care. For more information, see <http://grants1.nih.gov/grants/guide/rfa-files/RFA-RM-07-007.html>.

2007 NIH Director's New Innovator Award Program

As part of its commitment to increasing the success of new investigators, NIH created an award program this year to support highly innovative, high-impact approaches to significant problems in biomedical and behavioral research. The New Innovator Award program complements the more traditional R01 mechanism, which continues to be the primary source of funding for new investigators. For more information, see http://grants.nih.gov/grants/new_investigators/innovator_award/.

NIH Blueprint for Neuroscience Research

The Neuroscience Blueprint (<http://braininfo.us/blueprint/index.html>) is a framework to enhance cooperation among the 15 NIH ICs that support research on the nervous system. Created in 2004, the Blueprint already has a number of cross-cutting projects funded, from training initiatives to support for knockout mouse resources. The Blueprint will focus on neurodegeneration in 2007, neural development in 2008, and neural plasticity in 2009. Since January, several activities under the Blueprint have moved forward:

Neuroplasticity Workshop Team

Team Leaders: Nancy Pilotte, National Institute on Drug Abuse (NIDA); and Chiiko Asanuma, NIMH

To seek input from the extramural community on neuroplasticity initiative topics for Fiscal Year 2009 (FY09), the project team is planning a neuroplasticity workshop for August 2007. The team has issued a Request for Information (RFI) with a deadline of April 15:

<http://grants.nih.gov/grants/guide/notice-files/NOT-MH-07-106.html>.

Neurodevelopment Workshop Team

Team leaders: Beth-Anne Sieber, NIMH; and Bob Riddle, National Institute of Neurological Disorders and Stroke (NINDS)

Based on a neurodevelopment-focused workshop held in November 2006, several concepts are being developed.

Update on Electronic Submission

NIH achieved a smooth transition to electronic R01 submissions on February 5, 2007, though a few challenges arose for the March 5 resubmission/renewal R01 receipt date. Approximately 4,000 new R01s and 4,800 resubmission/renewal R01s were received. For more details, see <http://era.nih.gov/ElectronicReceipt/news.htm>.

Later in 2007, Grants.gov plans to have available a "New Grants.gov 2007 Solution," incorporating Adobe-based forms and Google search functionality. The new forms need

adequate testing before they can be deployed, but their deployment will be announced widely when the timeline is known. All funding opportunity announcements will be updated to link to the new forms when available. For more information, see the Electronic Submission web site at <http://era.nih.gov/ElectronicReceipt/index.htm>

NIMH Update

NIMH Director's Innovation Speaker Series

This speaker series focusing on innovation and creativity by encouraging broad, interdisciplinary thinking in the development of scientific initiatives and programs and to press for leaps in science over incremental thinking. Speakers since the start of 2007 have included:

- Sonja Schoenwald, PhD, Professor of Psychiatry and Behavioral Sciences at the Medical University of South Carolina – Innovations in the Effectiveness of Care: Getting What We Know How to Do to Those Who Need to Do It
- Freeman A. Hrabowski, III, PhD, President of the University of Maryland, Baltimore County – Thinking Differently to Beat the Odds: Preparing Minorities for Biomedical Research Careers
- Geoffrey Duyk, MD, PhD, Partner and Managing Director for TPG Growth – Lost in Translation: Adoption vs. Innovation
- Miguel A.L. Nicolelis MD, PhD, Anne W. Deane Professor of Neuroscience, Co-Director of the Center for Neuroengineering, and Professor of Neurobiology, Biomedical Engineering, and Psychological and Brain Sciences at Duke University – Computing with Neural Ensembles

Refining and Testing Interventions and Service Delivery Models for Youths Transitioning to Adulthood

The mental health problems and related impairment that many youth experience during the transition to adulthood are associated with a host of negative outcomes. However, care for individuals in this age range is complicated by the unique developmental context, the multi-problem nature of behavioral health conditions, the lack of age-adjusted, evidence-based interventions and services, and various discontinuities in service systems and health care financing. In the fall of 2006, the NIMH Division of Services and Interventions Research (DSIR) launched an initiative (<http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-07-050.html>) aiming to stimulate research on refining and testing interventions in service delivery models for youth transitioning to adulthood. Applications for this initiative were reviewed in March 2007 and discussed at the May 2007 Council meeting. Funded projects will address critical gaps in the research literature and may eventually help inform interventions and service delivery strategies for this important but often neglected age group.

Basic and Translational Research Opportunities in the Social Neuroscience of Mental Health

Through this program announcement (<http://grants.nih.gov/grants/guide/pa-files/PA-06-389.html>), NIMH seeks to stimulate basic and translational research into the neurobiological substrates of social behavior with the ultimate goal that findings derived from such investigations will provide greater insight into mechanisms of psychiatric disorders with known deficits in social behavior. The first round of applications was reviewed in March, and the results will be presented at the

May Council meeting. This initiative will run for two additional years; the next application receipt deadline is September 25, 2007.

Autism Centers of Excellence (ACE)

With the expiration of two autism centers programs—Studies to Advance Autism Research and Treatment (STAART) and Collaborative Program of Excellence in Autism (CPEA)—in 2007 and 2008, NIH created the unified ACE program in order to maximize coordination and cohesion of NIH-sponsored autism research efforts. In December 2005, two RFAs were issued to solicit applications for centers and networks, with an application deadline in August 2006. An ACE center involves collaborations of basic and clinical scientists conducting separate research projects that focus on a common unifying theme. An ACE network is a multi-site collaboration including one or more collaborative projects with a focus on a specific topic of research that requires multiple sites for optimal design and conduct of studies. NIH expects to award the ACE centers and networks in FY07 and FY08. The ACE programs will focus on a broad range of autism-related research, including but not limited to, neuroimaging, biomarkers and susceptibility genes, pharmacotherapy, early intervention, and risk and protective factors.

Science of Note

Study Sheds Light on Medication Treatment Options for Bipolar Disorder

Antidepressant medications are no more effective than a placebo (sugar pill) for treating depression in people with bipolar disorder who already are taking mood-stabilizing medications, according to Gary Sachs, Massachusetts General Hospital, and colleagues involved in the large-scale, multi-site Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Bipolar disorder is marked by severe, sometimes debilitating, mood swings between depression and mania, and finding the right treatment can be a challenge. The disorder is usually treated with mood stabilizers, such as lithium, or other medications that reduce mania. Antidepressant medications are often added to treat bipolar depression, but they may trigger a switch from depression to mania. In this study, doctors adjusted participants' mood stabilizer doses to optimal levels before participants were randomly assigned to take one of two antidepressants—bupropion (Wellbutrin) or paroxetine (Paxil)—or a placebo, in addition to the mood stabilizer. After about 26 weeks, there was no difference in the rate of recovery, stringently defined as staying well for eight consecutive weeks; roughly one out of four participants in both groups recovered. Antidepressants did not trigger a manic switch any more than placebo (about 10 percent in each group). Compared to each other, both antidepressants showed similar rates of response and manic switch. Future STEP-BD results will shed light on other treatment options for people with bipolar disorder.

Sachs GS, Nierenberg AA, Calabrese JR, Marangell LB, Wisniewski SR, Gyulai L, Friedman ES, Bowden CL, Fossey MD, Ostacher MJ, Ketter TA, Patel J, Hauser P, Rapport D, Martinez JM, Allen MH, Miklowitz DJ, Otto MW, Dennehy EB, Thase ME. Effectiveness of Adjunctive Antidepressant Treatment for Bipolar Depression. N Engl J Med. 2007 Mar 28; [Epub ahead of print]

Intensive Psychotherapy More Effective Than Brief Therapy for Bipolar Depression

People receiving medication treatment for bipolar disorder are more likely to get well faster and stay well if they also receive intensive psychotherapy, according to a STEP-BD study led by David Miklowitz of the University of Colorado. Psychotherapy is routinely used in conjunction

with medication to treat bipolar illness, but its effectiveness has been unclear. To address this issue, the researchers evaluated three types of standardized, intensive, nine-month-long psychotherapy compared to a control group that received a three-session, psychoeducational program called collaborative care. The intensive therapies were:

- family-focused therapy, which required the participation and input of patients' family members and focused on enhancing family coping, communication, and problem-solving;
- cognitive behavioral therapy, which focused on helping the patient understand distortions in thinking and activity, and learn new ways of coping with the illness; and
- interpersonal and social rhythm therapy, which focused on helping the patient stabilize his or her daily routines and sleep/wake cycles, and solve key relationship problems.

All participants were already taking medication for bipolar disorder. Over the course of a year, 64 percent of those in the intensive psychotherapy groups became well, compared with 52 percent of those in collaborative care. Patients in intensive psychotherapy became well an average of 110 days faster and were one and a half times more likely to be clinically well during any month out of the study year than those who received collaborative care. Discontinuation rates among the groups were similar. None of the three intensive psychotherapies appeared to be significantly more effective than the others, although rates of recovery were higher among those in family-focused therapy compared to the other groups.

Miklowitz DJ, Otto MW, Frank E, Reilly-Harrington NA, Wisniewski SR, Kogan JN, Nierenberg AA, Calabrese JR, Marangell LB, Gyulai L, Araga M, Gonzalez JM, Shirley ER, Thase ME, Sachs GS. Psychosocial treatments for bipolar depression: a 1-year randomized trial from the systematic treatment enhancement program. Arch Gen Psychiatry. 2007 Apr;64(4):419-26.

Brain's Electrical Signals Differ in Extreme Irritability and Childhood Bipolar Disorder

Defining pediatric bipolar disorder is a major issue in psychiatry because the disorder tends to be severe in this age group, and the rate of diagnosed cases appears to be rising. The classic definition includes extreme mood swings ranging from mania—over-excited, elated moods and irritability—to depression. Children with a similar illness called severe mood dysregulation (SMD) are also extremely irritable and hyperactive, but do not have clear-cut manic episodes. Some researchers maintain that pediatric bipolar disorder should be broadly defined to include SMD, an assertion countered by a study led by NIMH researcher Brendan Rich. The scientists obtained electroencephalograms (EEGs), or brain activity scans, of 35 children with classic bipolar disorder, 21 children with SMD, and 26 healthy children (average age 12 to 13) while they performed a task repeatedly; each time they did the task, they won or lost 10 cents. The task was frustrating because the children often lost money. While both the children with bipolar disorder and those with SMD became more frustrated than did healthy children performing the same task, the brain mechanisms associated with their frustration differed. Children with bipolar disorder had an abnormality in the brain's ability to purposefully direct attention, but children with SMD had abnormalities in brain signals that occur when a stimulus grabs someone's attention. The new study shows that, some day, doctors could use biological measurements, such as EEGs, to help make psychiatric diagnoses, in combination with clinical symptoms.

Rich BA, Schmajuk M, Perez-Edgar KE, Fox NA, Pine DS, Leibenluft E. Different psychophysiological and behavioral responses elicited by frustration in pediatric bipolar disorder and severe mood dysregulation. Am J Psychiatry. 2007 Feb;164(2):309-17.

Genetic Roots of Bipolar Disorder Revealed by First Genome-Wide Study of Illness

The likelihood of developing bipolar disorder depends in part on the combined, small effects of variations in many different genes in the brain, none of which is powerful enough to cause the disease by itself, shows a new study led by NIMH researcher Francis J. McMahon and colleagues. However, targeting the enzyme produced by one of these genes could lead to development of new, more effective medications. Enabled by recent genetics technology that allows researchers to scan, in a single experiment, thousands of genes for variations, this study was the first to scan virtually all of the variations in human genes to find those associated with bipolar disorder, and is part of the NIMH Genetics Initiative. In this study, researchers compared variations found in the scans of 413 adults who had bipolar disorder with variations found in the scans of 563 healthy adults. One of the genes correlated with the disorder, *DGKH*, is active in a biochemical pathway through which lithium, the primary treatment for bipolar disorder, is thought to exert its therapeutic effects. The gene produces an enzyme (diacylglycerol kinase eta) that functions at a point closer to the root of the lithium-sensitive pathway than does lithium itself. Several other genes detected in the study produce proteins involved in this and other biochemical pathways thought to play a role in bipolar disorder. Understanding the effects that variations of these genes have on brain-cell function could lead to explanations of how they contribute to the condition and how it might be better prevented or treated.

Baum AE, Akula N, Cabanero M, Cardona I, Corona W, Klemens B, Schulze TG, Cichon S, Rietschel M, Nöthen MM, Georgi A, Schumacher J, Schwarz M, Jamra RA, Höfels S, Propping P, Satagopan J, NIMH Genetics Initiative Bipolar Disorder Consortium, Detere-Wadleigh SD, Hardy J, McMahon F. A genome-wide association study implicates diacylglycerol kinase eta (DGKH) and several other genes in the etiology of bipolar disorder. Mol Psychiatry. 2007 May 8. [Epub ahead of print].

Gene Knockout Unleashes Manic Mouse

Mice engineered to lack a gene that codes for the CLOCK protein showed behaviors similar to human mania in a study by Colleen McClung, University of Texas, and colleagues. Similar to the people in the manic phase of bipolar disorder, the mice experienced disruption of daily rhythms—sleep, appetite, activity—known to be regulated in part by the CLOCK protein. The engineered rodents also seemed wired for reward-seeking. They required lower-than-normal levels stimulation to activate their brain reward circuitry, showed heightened reward-related and performance-enhancing effects with cocaine, and gorged on sugar. People with mania also tend to engage in risky reward-seeking behavior. In another similarity to manic humans, the mice seemed relatively anxiety-free. They ventured where mice normally fear to tread—lingering in an unprotected open environment 13 times longer than usual. They were also undaunted by stressful situations that typically trigger depression-like reactions. The researchers noted increased activity of the brain chemical messenger dopamine in the ventral tegmental area, hub of a key brain reward circuit. As with bipolar disorder patients, lithium treatment, known to reduce dopamine in this area, restored the aberrant mouse behaviors to normal. Restoring normal functioning of the CLOCK protein also led to more normal behavior. The new mouse model holds promise for understanding CLOCK's workings in mania not only in reward circuitry, but also in pathways that regulate circadian rhythms.

Roybal K, Theobald D, Graham A, Dinieri JA, Russo SJ, Krishnan V, Chakravarty S, Peevey J, Oehrlein N, Birnbaum S, Vitaterna MH, Orsulak P, Takahashi JS, Nestler EJ, Carlezon WA Jr, McClung CA. From the Cover: Mania-like behavior induced by disruption of CLOCK. Proc Natl Acad Sci USA. 2007 Apr 10;104(15):6406-11.

Two Types of Neurons Help Regulate Sleep/Wake State

One of the most intriguing questions in sleep research relates to the nature and function of neurons involved in regulating sleep and arousal states. Previous evidence suggested certain sleep-activated neurons that interact with a specific region of the lateral hypothalamus called the median preoptic area may be involved, as these cells become active before sleep and during various phases of sleep. Dennis McGinty, of the Veterans Affairs Greater Los Angeles Healthcare System, and colleagues tested whether the electrical and chemical manipulating sleep-activated neurons in the median preoptic area affect regulation of the dynamic balance between wake and sleep within the hypothalamus. To measure any effects, the researchers implanted freely moving rats with special electrodes that can detect changes in neuronal activity within the brain. The results show that both electrical and chemical stimulation of the median preoptic area increases activity of sleep-related hypothalamic neurons and inhibits activity of wake-related hypothalamic neurons. In contrast, inactivation of the median preoptic area neurons produced the opposite effect; sleep-related hypothalamic neurons were suppressed while wake-related neurons were excited. This study provides novel evidence that two different types of median preoptic neurons regulate the dynamic switch between sleep and wake states in the hypothalamus. Such research can help further the understanding of how disturbances in sleep dynamics occur in PTSD and mood disorders.

Suntsova N, Guzman-Marin R, Kumar S, Alam MN, Szymusiak R, McGinty D. The median preoptic nucleus reciprocally modulates activity of arousal-related and sleep-related neurons in the perifornical lateral hypothalamus. J Neurosci. Feb 14, (27) (7) 1616-30, 2007.

New Details in Schizophrenia Treatment Trial Emerge

Two new studies from the Clinical Antipsychotic Trials for Intervention Effectiveness (CATIE) provide more insights into comparing treatment options, and to what extent antipsychotic medications help people with schizophrenia with everyday functioning in the community. In one study, T. Scott Stroup, of the University of North Carolina at Chapel Hill, and colleagues compared the effectiveness of three atypical antipsychotic medications by determining how long patients stayed on their assigned medication after having previously discontinued an older antipsychotic. Those taking quetiapine (Seroquel) stayed on the longest, averaging about ten months before discontinuing. Those taking olanzapine (Zyprexa) discontinued after an average of about seven months, and participants taking risperidone (Risperdal) discontinued after an average of four months. None of those taking quetiapine discontinued use due to weight gain or metabolic side effects, but 13 percent of participants assigned to olanzapine treatment did so, as well as five percent of those on risperidone.

The second study, led by Marvin Swartz of Duke University, evaluated the social and vocational functioning, interpersonal relationships, and psychological well-being of 455 participants—about one-third of the CATIE study population. Those who stuck with their initial antipsychotic treatment showed some improvement in functioning, and there were no differences among the medications in making these gains. The greatest gains were seen in participants with the poorest community living skills at the beginning of the study, but they were also more likely to discontinue treatment early in the process. Swartz and colleagues posit that participants encountered a “ceiling effect” at which point additional psychosocial skill improvement was unlikely without additional rehabilitative treatment. Their findings support the need for a

combination of medication and dedicated rehabilitative services in order to help people with schizophrenia learn to function in the community.

Stroup TS, Lieberman JA, McEvoy JP, Swartz MS, Davis SM, Capuano GA, Rosenheck RA, Keefe RS, Miller AL, Belz I, Hsiao JK; CATIE Investigators. Effectiveness of olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia after discontinuing perphenazine: a CATIE study. Am J Psychiatry. 2007 Mar;164(3):415-27.

Swartz MS, Perkins DO, Stroup TS, Davis SM, Capuano G, Rosenheck RA, Reimherr F, McGee MF, Keefe RS, McEvoy JP, Hsiao JK, Lieberman JA; CATIE Investigators. Effects of antipsychotic medications on psychosocial functioning in patients with chronic schizophrenia: findings from the NIMH CATIE study. Am J Psychiatry. 2007 Mar;164(3):428-36.

Weight Gain From Antipsychotics Traced to Appetite-Regulating Enzyme

A likely mechanism by which antipsychotic medications trigger weight gain—with its attendant risks of heart disease, diabetes, and treatment non-adherence—was recently unraveled by Solomon Snyder, of Johns Hopkins University, and colleagues. In mice, the scientists demonstrated that the atypical antipsychotic clozapine (Clozaril) increased the appetite-regulating enzyme AMPK four times more than normal in hypothalamus regions controlling feeding. In untreated mice, AMPK was reduced after the animals were given the appetite-suppressing hormone leptin. However, when given clozapine, AMPK increased even in the presence of leptin. Following up on earlier clues, the researchers also found that blocking the receptor for the messenger chemical histamine mimicked clozapine's effect, boosting AMPK activation. Mice genetically engineered to lack the histamine receptor showed no increase in AMPK in response to clozapine. This confirmed that the receptor is likely the important link in the appetite-stimulating effect of atypical antipsychotic medications. In addition to the implications for design of newer antipsychotics, the findings may also lead to new strategies in weight and appetite control research, add the researchers.

Kim SF, Huang AS, Snowman AM, Teuscher C, Snyder SH. From the Cover: Antipsychotic drug-induced weight gain mediated by histamine H1receptor-linked activation of hypothalamic AMP-kinase. Proc Natl Acad Sci USA. 2007 Feb 27;104(9):3456-9.

Common Gene Version Optimizes Thinking – But With a Possible Downside

Most people inherit a version of a gene that optimizes their brain's thinking circuitry, yet also appears to increase risk for schizophrenia, a severe mental illness marked by impaired thinking. The seeming paradox emerged from the first study, led by NIMH researcher Daniel Weinberger, to explore the effects of variation in the human gene for a brain master switch, DARPP-32. To understand DARPP-32's role in the human brain, the research team used various techniques to identify the gene variants and their functional consequences. The researchers also identified a common version of the gene and showed how it impacts the way two key brain regions exchange information, affecting a range of functions from general intelligence to attention. Three-fourths of subjects studied had at least one copy of the version that results in more efficient filtering of information processed by the brain's executive hub, the prefrontal cortex. However, the same version was also more prevalent among people who developed schizophrenia. This study builds on past research suggesting a link between DARPP-32 and schizophrenia.

Meyer-Lindenberg A, Straub RE, Lipska BK, Verchinski BA, Goldberg T, Callicott JH, Egan MF, Huffaker SS, Mattay VS, Kolachana B, Kleinman JE, Weinberger DR. Genetic evidence implicating DARPP-32 in human frontostriatal structure, function, and cognition. J Clin Invest. 2007 Mar;117(3):672-82.

Benefits of Antidepressants May Outweigh Risks for Kids

In 2004, the U.S. Food and Drug Administration (FDA) required a “black box” warning—the most serious type of warning—on all antidepressant medications after a thorough review revealed a slight increase in suicidal thoughts and actions among children and adolescents taking antidepressants, compared to those taking a placebo. To put this finding in the context of how to treat young patients, David Brent, of Western Psychiatric Institute & Clinic in Pennsylvania, and colleagues examined data from 27 clinical trials conducted between 1988 and 2006. They focused on trials of participants younger than age 19 who were being treated with antidepressants for major depression, obsessive-compulsive disorder (OCD), or non-OCD anxiety disorders such as generalized anxiety disorder or social phobia. They also reviewed data from more recent trials that were not included in the FDA analysis. By pooling the data, the researchers found that antidepressants were significantly more effective than placebo. Antidepressants were especially effective in treating non-OCD anxiety disorders, and showed more modest results for those with OCD or depression. Overall, there was a slight but statistically significant increase in the risk of suicidal thoughts and actions, but no suicides occurred. The researchers suggest that the benefits of treating young people with antidepressants are far greater than the risks for suicidal thoughts or actions, and that future studies should focus on methods for monitoring young patients, to put both doctors and parents at ease, and to match patients with the best treatments.

Bridge JA, Iyengar S, Salary CB, Barbe RP, Birmaher B, Pincus HA, Ren L, Brent DA. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. JAMA. 2007 Apr 18;297(15):1683-96.

Cognitive Therapy As Effective As Medication in Second Try to Treat Depression

Latest results from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial found that switching to or adding cognitive therapy (CT) after a first unsuccessful attempt at treating depression with an antidepressant medication is generally as effective as switching to or adding another medication. However, remission may take longer to achieve. In Level 2 of STAR*D, participants had the option of either switching to a new treatment (switch group) or continuing to take the Level 1 medication citalopram while adding another treatment (add-on group). Those in the switch group had the option of trying either CT or one of three antidepressants. Participants in the add-on group could add CT to their citalopram, or they could add a different antidepressant medication to their citalopram. Ultimately, 147 participants either switched to CT, or added it as an adjunctive treatment to citalopram. About 25 percent of those who switched to CT alone, and about 23 percent of those who added it, became symptom-free. The rates were not significantly different from those who were in medication-only treatment pathways in Level 2, suggesting that CT was generally as effective as medication as a second step in treating depression. However, among those in the CT add-on group, remission took longer to achieve—an average of 55 days—compared with an average of 26 days among those who added another medication.

*Thase ME, Friedman ES, Biggs MM, Wisniewski SR, Trivedi MH, Luther JF, Fava M, Nierenberg AA, McGrath PJ, Warden D, Niederhe G, Hollon SD, Rush AJ. Cognitive Therapy as a Second-step Treatment: A STAR*D Report. Am J Psychiatry. 2007 May;164(5):753-60.*

Virtual-Reality Video Game Helps Link Depression to Specific Brain Area

A video game that challenges spatial memory, the type that helps people navigate around town, may be a powerful new tool to help assess the link between depression and the hippocampus, the brain’s memory hub. In a study led by NIMH researcher Carlos Zarate, depressed people

performed poorly on the game when compared with nondepressed people. This study strengthened the evidence of a link between the hippocampus and depression by showing that people with hippocampus dysfunction—as revealed by spatial memory problems detected by the new video game—are more likely to be depressed. The researchers suggested that the virtual-reality, three-dimensional aspects of the video game engage areas of the hippocampus that the two-dimensional test traditionally used in such studies does not. The game, developed by scientists at the University College of London, may point the way to new treatments for depression. With further development, it could also help scientists track biological and environmental factors that play a role in the illness.

Gould NF, Holmes MK, Fantie BD, Luckenbaugh DA, Pine DS, Gould TD, Burgess N, Manji HK, Zarate CA Jr. Performance on a virtual reality spatial memory navigation task in depressed patients. Am J Psychiatry. 2007 Mar;164(3):516-9.

African Americans, Black Caribbeans, and Whites Differ in Depression Risk, Treatment

Although black Americans are less likely than whites to have a major depressive disorder (MDD), when they do, it tends to be more chronic and severe. They are also much less likely to undergo treatment, according to David R. Williams and colleagues from the University of Michigan and Wayne State University. The researchers' data from the National Survey of American Life (NSAL) shows striking differences among black subgroups; fewer than half of African Americans with MDD undergo treatment, but the rate drops to about one-quarter in Caribbean blacks who emigrated to or were born in the United States. Education and income were not linked to risk of MDD in any group, but some other variables were. For example, older African Americans and whites were less likely to have had MDD than were younger people. Almost all respondents, regardless of race, said MDD interfered with their home, work, or social lives or relationships. Among those who were severely impaired, African Americans and Caribbean blacks reported being unable to function in their daily lives for slightly more days of the year than whites (71 vs. 63 days). Treatment rates among African American and Caribbean black populations were also lower than previously reported rates for the general population. These findings highlight the urgent need for a better understanding of the factors that may lead to health disparities and implementing interventions to eliminate such disparities.

Williams DR, Gonzalez HM, Neighbors H, Nesse R, Abelson JM, Sweetman J, Jackson JS. Prevalence and distribution of major depressive disorder in African Americans, Caribbean blacks, and non-Hispanic whites: results from the National Survey of American Life. Arch Gen Psychiatry. 2007 Mar;64(3):305-15.

Depression Risk Higher in Girls with Low Birth Weight

Girls' risk for developing depression after puberty increased significantly if they had low birth weight, which seemed to increase the risk effects of other adversities, according to E. Jane Costello of Duke University, and colleagues. Among the 5.7 percent of girls in their study with low birth weight, more than 38 percent developed at least one episode of depression as teens, compared to only 8.4 percent with normal birth weight. Having one or more other risk factors for depression in addition to low birth weight greatly increased the chances of a teenage girl developing the illness compared to normal birth weight girls. But if she had no other risk factors, low birth weight posed no additional risk. Nor did it increase depression risk in teenage boys; boys are more prone to low birth weight, but fewer than five percent of low birth weight teenage boys became depressed—about the same rate as other boys. According to the researchers, these findings suggest that pediatricians and parents of girls who were of low birth weight should pay close attention to their mental health as they enter puberty.

Costello EJ, Worthman C, Erkanli A, Angold A. Prediction from low birth weight to female adolescent depression: a test of competing hypotheses. *Arch Gen Psychiatry*. 2007 Mar;64(3):338-44.

Tiny, Spontaneous Gene Mutations May Boost Autism Risk

Tiny gene mutations, each individually rare, pose more risk for autism than had been previously thought, suggest Jonathan Sebat and Michael Wigler, both of Cold Spring Harbor Laboratory, and colleagues. Using new, high-resolution array technology to detect mutations that were present in a child but not in either parent, the researchers screened genetic material from 264 families. These families were drawn, in part, from the Autism Genetic Resource Exchange (AGRE) and the NIMH Center for Collaborative Genetic Studies of Mental Disorders. Spontaneous deletions and duplications of genetic material were found to be 10 times more prevalent in sporadic cases of autism spectrum disorders than in healthy control subjects—but only twice as prevalent in autism cases from families with more than one affected member. The sporadic form of autism accounts for 90 percent of affected individuals. The results implicate the anomalies as primary, rather than just contributory, causes of the disorder in most cases when they are present, and support the existence of two, different, genetic mechanisms that contribute to risk: spontaneous mutation and inheritance. The researchers further suggested using different genetic approaches and increasing recruitment of families in which only one person has the disorder in order to better understand sporadic autism.

Sebat J, Lakshmi B, Malhotra D, Troge J, Lese-Martin C, Walsh T, Yamrom B, Yamrom B, Yoon S, Krasnitz A, Kendall J, Leotta A, Pai D, Zhang R, Lee YH, Hicks J, Spence SJ, Lee AT, Puura K, Lehtimäki T, Ledbetter D, Gregersen PK, Bregman J, Sutcliffe JS, Jobanputra V, Chung W, Warburton D, King MC, Skuse D, Geschwind DH, Gilliam TC, Ye K, Wigler M. Strong Association of De Novo Copy Number Mutations with Autism. *Science*. 2007 Mar 15; [Epub ahead of print]

Half of Adults With Anxiety Disorders Had Psychiatric Diagnoses in Youth

Anxiety disorders—which include panic disorders, OCD, phobias, and other disorders—are among the most common psychiatric illnesses, with around 29 percent of American adults diagnosed with one or more at some point in life. In this study, researchers led by Alice M. Gregory and Terrie Moffitt, both of King's College London, examined the psychiatric histories of 1,037 adults, ages 11–32. About half of adults with an anxiety disorder had symptoms of some type of psychiatric illness by age 15. The researchers also found that some of the specific illnesses detected in youth were clues as to the kinds of anxiety disorders they would have as adults. For example, adults with PTSD had histories of extreme defiance and conduct disorders in childhood. Adults with OCD tended to have had delusional beliefs and hallucinations as children. Phobias in adulthood tended to be linked to specific phobias that occurred during childhood. The results underscore the importance of early diagnosis and prevention of anxiety disorders, and suggest that different anxiety disorders may have different roots.

Gregory AM, Caspi A, Moffitt TE, Koenen K, Eley TC, Poulton R. Juvenile mental health histories of adults with anxiety disorders. *Am J Psychiatry*. 2007 Feb;164(2):301-8.

Early Separation from Mother Affects Genes Related to Social and Emotional Behavior

Compared to children raised by one or more parent, children separated from their parents early in life are more vulnerable to developing psychiatric disorders, more likely to engage in self-comforting behavior, and less likely to seek out social comfort. A recent study by Karoly Mirnics, of Vanderbilt University, and colleagues sought to identify the brain systems underlying social deficits associated with parental separation and whether there were differences in the expression of particular genes associated with neural function in these systems. Monkeys

separated from their mothers at one week or one month of age were compared with maternally-reared controls for differences in gene expression within several brain regions. One gene in particular, guanylate cyclase 1 alpha 3 (GUCY1A3), showed decreased expression in the one week versus one month maternally-separated and control animals. GUCY1A3 is part of an important signaling pathway in neurons within the amygdala, a brain structure critical for emotional and social behavior, and other brain regions. Decreased expression in the early maternally-separated group was shown to be specifically due to the effects of separation, and the level of expression was correlated with abnormalities in social behaviors. The study results demonstrate how early life stressors can affect the expression of genes that are important for normal social and emotional behavior. Understanding the behavioral and neural effects of altered gene function provides insight into potential therapeutic targets and has significant implications for how and when anxiety and emotional disorders develop.

Sabatini MJ, Ebert P, Lewis DA, Levitt P, Cameron JL, Mirnics K. Amygdala gene expression correlates of social behavior in monkeys experiencing maternal separation. J Neurosci. 2007 March 21; 27(12):3295-3304.

Treatment Selectively Eliminates Fearful Memories

The brain first records experiences as fleeting short-term memories. Some short-term memories later become more stable through a process called consolidation, which involves building new proteins. When these long-term memories are recalled, they again become vulnerable; new proteins must be produced to reconsolidate retrieved memories and return them to long-term storage. To see if specific long-term memories could be eliminated during retrieval, Joseph LeDoux, of New York University, and colleagues trained rats to fear two different musical tones by following the tones with a mild electric shock to the foot. Some rats then received either a drug known as U0126, which blocks production of proteins needed for memory reconsolidation, or an inactive substance for comparison. A half-hour after the treatments, rats were again exposed to just one of the sounds, this time without a shock. When both tones were played the following day, the treated rats showed no fear of the tone they had heard while under the influence of U0126, yet still reacted with fear to the other tone. However, untreated rats froze with fear upon hearing either tone. These findings suggest that two similar fear-associated memories can be independently recollected, modified, and reconsolidated, even when they both share the same unpleasant expectation. Although U0126 is not approved for human use, certain prescription drugs, like propranolol, are known to affect memory reconsolidation in humans. These clinically approved medications may also hold potential for selectively blocking fearful memories, and could be useful to treat PTSD and other memory-related conditions.

Doyere V, Debiec J, Monfils MH, Schafe GE, LeDoux JE. Synapse-specific reconsolidation of distinct fear memories in the lateral amygdala. Nat Neurosci. 2007 Apr; 10 (4): 414-416.

Adolescent Brains Show Lower Activity in Areas That Control Risky Choices

When contemplating risky decisions, adolescents show less activity in regions of the brain that regulate processes involved in decision-making, compared with adults. The areas—the orbitofrontal/ventrolateral prefrontal cortex and dorsal anterior cingulate cortex—are among the last to develop and are involved in control of “thinking” functions, including decision-making, and in processing reward-related input and behavior. In a study by NIMH researcher Monique Ernst and colleagues, 16 adolescents and 14 adults played a game of chance. At each turn, they could choose a high-risk or low-risk option to try to win. The high-risk option offered greater reward than the low-risk option, but the chance of winning was much lower. Scientists measured brain activity while the participants made their choices using technology called functional

magnetic resonance imaging (fMRI). The results suggest that when it comes to making choices involving risk, adolescents do not engage the higher-thinking, decision-and-reward areas of the brain as much as adults do. Brain development continues throughout adolescence, and the reduced activity seen in specific areas in the healthy adolescents in this study appears to be normal. Such studies help researchers map normal maturation in the brain. This data can then be used for comparison in studies of mental illnesses, some of which begin during adolescence, including depression and anxiety disorders.

Eshel N, Nelson EE, Blair RJ, Pine DS, Ernst M. Neural substrates of choice selection in adults and adolescents: development of the ventrolateral prefrontal and anterior cingulate cortices. Neuropsychologia. 2007 Mar 25;45(6):1270-9.

U.S.-born Children of Immigrants at Higher Risk for Mental Disorders Than Parents

Early findings from the NSAL and the National Latino and Asian American Study (NLAAS) show that immigrants in general appear to have lower rates of mental disorders than their U.S.-born counterparts. However, risks for particular disorders may differ depending on ethnic subgroup, gender, English-language proficiency, years of living in the United States, and age at immigration. Patterns of mental health service use also varied among the different groups, but overall, U.S.-born children and grandchildren of immigrants showed greater service use than immigrants themselves. Among the diverse ethnic subgroups, the researchers also observed differences in patterns of service use according to a variety of ethnic- and immigration-related factors. Both the NSAL and NLAAS are the largest studies of their kind to date and are part of the NIMH-supported Collaborative Psychiatric Epidemiological Survey program, which also included the National Comorbidity Survey Replication. Together, these national surveys provide improved data on the mental health of racial and ethnic minorities living in the United States. Such research is critical for developing programs and services that meet the specific needs of minority populations and may help reduce current health care disparities.

Boyce CA, Cain VS. Disentangling Health Disparities Through National Surveys. Am J Public Health. 2007 Jan;97(1):10.

Takeuchi DT, Alegria M, Jackson JS, Williams DR. Immigration and Mental Health: Diverse Findings in Asian, Black, and Latino Populations. Am J Public Health. 2007 Jan;97(1):11-2.

Williams DR, Haile R, Gonzales HM, Neighbors H, Baser R, Jackson JS. The Mental Health of Black Caribbean Immigrants: Results from the National Survey of American Life. Am J Public Health. 2007 Jan;97(1):52-9.

Jackson JS, Neighbors HW, Torres M, Martin LA, Williams DR, Baser R. Use of Mental Health Services and Subjective Satisfaction With Treatment Among Black Caribbean Immigrants: Results from the National Survey of American Life. Am J Public Health. 2007 Jan;97(1): 60-7.

Alegria M, Mulvaney-Day N, Torres M, Polo A, Cao Z, Canino G. Prevalence of Psychiatric Disorders Across Latino Subgroups in the United States. Am J Public Health. 2007 Jan;97(1):68-75.

Alegria M, Mulvaney-Day N, Woo M, Torres M, Gao S, Oddo V. Correlates of Past-Year Mental Health Service Use Among Latinos: Results From the National Latino and Asian American Study. Am J Public Health. 2007 Jan;97(1):76-83.

Takeuchi DT, Zane N, Hong S, Chae DH, Gong F, Gee GC, Walton E, Sue S, Alegria M. Immigration-Related Factors and Mental Disorders Among Asian Americans. Am J Public Health. 2007 Jan;97(1):84-90.

Abe-Kim J, Takeuchi DT, Hong S, Zane N, Sue S, Spencer MS, Appel H, Nicdao E, Alegria M. Use of Mental Health-Related Services Among Immigrant and US-Born Asian Americans: Results from the National Latino and Asian American Study. Am J Public Health. 2007 Jan;97(1):91-8.

Global Use of ADHD Medications Rises Dramatically

Global use of medications that treat attention deficit/hyperactivity disorder (ADHD), including amphetamine (Adderall), methylphenidate (Concerta, Ritalin), and atomoxetine (Strattera), nearly tripled from 1993 to 2003, and spending on the drugs rose nine-fold, according to a study by Richard Scheffler, of the University of California-Berkeley, and colleagues. Using an international pharmaceutical database, the researchers examined data from nearly 70 countries, mostly from North America, Europe, and Northeast Asia. They found that among 5- to 19-year-olds, use of medications prescribed to treat ADHD increased by 274 percent. The United States prescribes the most, but its share of the worldwide market declined from 87 percent in 1993 to 83 percent in 2003. Global expenditures on ADHD medications also increased—from less than \$300 million in 1993 to \$2.4 billion in 2003, adjusted for inflation. The study confirmed that the United States remains the leading consumer of ADHD medications by wide margins. But other high-income countries, particularly Canada and Australia, showed higher-than-expected increases in ADHD medication use, and countries with modest use showed increases as well. In addition, more countries have begun to use the medications—from 31 in 1993 to 55 in 2003. Given these results, the study authors recommend clearly identifying the benefits and risks of these pharmacologic treatments, and promoting careful prescribing and monitoring practices. Scheffler RM, Hinshaw SP, Modrek S, Levine P. *The global market for ADHD medications.* Health Aff (Millwood). 2007 Mar-Apr;26(2):450-7.

Treatment May Help Reduce Severity of Mental Impairment in HIV-Infected Children

During the first few years of life, children born with HIV infection are most susceptible to central nervous system (CNS) disease, and can develop impaired cognitive, language, motor, and behavioral functioning. However, Kathleen Malee of Northwestern University and colleagues found that among children with HIV infection, treatment with a protease inhibitor (PI)-based highly active antiretroviral therapy (HAART) helped protect against cognitive and motor difficulties compared to a control group of age-matched children who were born to HIV-infected mothers but who did not contract the virus themselves (e.g., HIV-exposed). Before age one, HIV-infected children had lower mental and motor skills than their HIV-exposed counterparts. However, using standardized tests, the researchers found that the mental and motor skills of uninfected children appeared to decline with age—likely resulting from the complex interplay between genetic and environmental factors. In contrast, the mental skills of HIV-infected children declined less than expected, and their scores for motor skills actually improved slightly. HIV-infected children born prior to 1997 and who therefore did not receive PI-based HAART continued to decline in mental and motor skills. The results offer encouragement for treating infants and young children with HIV infection, who are at the highest risk for CNS disease and other neurodevelopmental difficulties. However, more research is needed to better understand how PI-based HAART intersects with other factors to affect neurodevelopment in these children. This research is part of a large-scale, longitudinal study conducted within the Pediatric AIDS Clinical Trials Group Network.

Lindsey JC, Malee KM, Brouwers P, Hughes MD; PACTG 219C Study Team. *Neurodevelopmental functioning in HIV-infected infants and young children before and after the introduction of protease inhibitor-based highly active antiretroviral therapy.* Pediatrics. 2007 Mar;119(3):e681-93.

Effective HIV Prevention Requires Behavioral Interventions, Not Just Treatment

Providing antiretroviral medications to HIV positive individuals is insufficient to control the HIV/AIDS epidemic and must be complemented by behavioral risk reduction interventions,

according to a study led by Alethea McCormick of Harvard School of Public Health, and colleagues. Using a simulated model that incorporated data collected from a long-term cohort study of HIV-infected men who have sex with men, the researchers determined that the use of antiretroviral drugs decreases the number of HIV transmissions that could be expected in the absence of treatment, particularly within the initial 10 years after infection. Over the span of a lifetime, however, the provision of treatment yields an estimated 23 percent increase in the total number of HIV transmissions, primarily by extending patient survival. The findings indicate that sustained efforts must be made to target behavioral risk reduction interventions to individuals living with HIV in order to achieve effective prevention.

McCormick AW, Walensky RP, Lipsitch M, Losina E, Hsu H, Weinstein MC, Paltiel AD, Freedberg KA, Seage GR 3rd. The effect of antiretroviral therapy on secondary transmission of HIV among men who have sex with men. Clin Infect Dis. 2007 Apr 15;44(8):1115-22.

Behavioral Intervention Reduces Risk Behavior Among People Living with HIV

People living with HIV (PLH) face a myriad of complications that accompany chronic illness, underscoring the need for ongoing “positive prevention.” Although many PLH reduce their risk after learning they are HIV-positive, some continue to engage in unprotected sexual behavior. In the largest randomized controlled trial to date on interventions to address this issue, investigators with the Healthy Living Project tested the efficacy of a cognitive-behavioral intervention in a diverse sample of 936 participants in four cities that carry a large portion of HIV burden in the United States. The primary aim of the 15-session, individually tailored intervention was to reduce the number of unprotected sexual encounters with HIV-negative partners or with those who don’t know their status. Overall, significant differences between the intervention and wait-list control participants were documented over a 25-month follow-up period, with the greatest reduction (36 percent) occurring 20 months post-intervention. This intervention, which addressed stress and coping needs, treatment adherence issues, and sexual risk-reduction, could serve as a model for personalized case-management services, especially within HIV treatment settings.

Healthy Living Project Team. Effects of a behavioral intervention to reduce risk of transmission among people living with HIV: the healthy living project randomized controlled study. J Acquir Immune Defic Syndr. 2007 Feb 1;44(2):213-21.

New NIMH Initiatives

NIMH-Administered RFAs

- *Innovative Trials for the Treatment of Anorexia Nervosa in Late Adolescence and Adulthood*

NIMH is seeking applications to support small-scale, innovative intervention development studies directed toward the treatment of Anorexia Nervosa (AN) in older adolescents and adults. Examples of research topics include strategies for weight gain and relapse prevention, optimal therapy delivery, efficacy studies to help tailor AN therapies, and novel psychosocial and/or pharmacological AN treatment strategies.

Release Date: March 22, 2007; Expiration Date: May 24, 2007

<http://grants1.nih.gov/grants/guide/rfa-files/RFA-MH-07-090.html>

Scientific Program Director: Mark Chavez, PhD, Division of Adult Translational Research & Treatment Development (DATR), NIMH

- *Prevention of Trauma Related Adjustment and Mental Disorders in High-Risk Occupations*

NIMH invites applications that will contribute directly to the goal of establishing empirically-demonstrated methods of preventing the development of trauma-related disorders among high trauma exposure occupational groups, for example, civilian employees and military personnel who regularly encounter traumatic situations. From a scientific perspective, occupations that involve exposure to trauma at higher than average frequency present unique opportunities for testing the effectiveness of preventive interventions designed to minimize posttraumatic adjustment disorders. From a public health and national security perspective, attending to the mental and behavioral health of individuals and groups who respond to emergencies, provide disaster relief, defend national interests, participate in peacekeeping missions, and maintain a civil society can be viewed as strengthening our national infrastructure. This RFA is being issued under the R01 and R34 mechanisms.

Release/Posted Date: April 12, 2007; Expiration Date: November 22, 2008

<http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-08-010.html>

<http://grants.nih.gov/grants/guide/rfa-files/RFA-MH-08-011.html>

Scientific Program Director: Farris K. Tuma, ScD, MHS, DATR, NIMH

Research Conferences and Workshops

Alliance for Research Progress – Winter Meeting

In January 2007, the NIMH Office of Community Relations and Public Liaison (OCRPL) convened the Winter Meeting of the Alliance for Research Progress. The Alliance is a group of representatives from patient and family-related advocacy organizations directly concerned with mental illnesses. Regular meetings provide opportunities for Alliance members to interact directly with Institute leadership, to learn about new research, to discuss changes in the field, and to network with colleagues. The winter meeting focused on two topic areas: children's mental health and the current state of mental health interventions. The Honorable Sue Myrick (R-NC) provided comments and the "View from Capitol Hill." *For more information, please contact Alison Bennett at abennet1@mail.nih.gov.*

Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia

In February 2007, NIMH sponsored this conference in Bethesda, Maryland to bring together basic and clinical cognitive neuroscientists, animal modelers from academia and industry, and clinical trial experts who share a common interest in developing neuroscience-based measures for assessing cognitive deficits in schizophrenia. Following invited talks by basic scientists and breakout groups involving all attendees, meeting participants recommended eight cognitive constructs for further measurement development within the areas of perception, attention, working memory, executive control, long term memory, and social-emotional processing. Subsequent meetings this fall and next spring will address psychometric issues in adapting cognitive neuroscience measures for clinical use and laboratory tasks of component cognitive processes that are ripe for clinical translation. *For more information, please contact Robert Heinsse at rheinsse@mail.nih.gov.*

AIDS Research Center Directors' Meeting

The NIMH Center for Mental Health Research on AIDS (CMHRA) held a Center Directors' meeting in March 2007 to review sites and plans for the future. The goals of the meeting included identifying a multi-site research agenda as well as a means of substantively fostering collaborative and creative research utilizing existing structures together with other HIV networks and structures. The behavioral science Center Directors identified areas of high priority, which included studying high-risk, HIV-negative, risk behavior compensation and modeling outcomes; and behavioral interventions. The basic science Center Directors proposed increasing efforts regarding the development of clinically useful predictive and surrogate biomarkers, developing animal models of HIV neuropathogenesis and treatments, conducting controlled clinical trials with novel designs or outcome measures, and developing therapies and outcome measures that could be applied in resource-limited settings. *For further information, please contact Dianne Rausch at drausch@mail.nih.gov.*

Second International Conference on HIV Treatment Adherence

In March 2007 in Jersey City, New Jersey, NIMH and the International Association of Physicians in AIDS Care (IAPAC) hosted a state-of-the-science conference focused on understanding and enhancing patient adherence to HIV treatment regimens. Nearly 400 researchers and health and human service professionals attended the conference, which profiled the most current HIV treatment adherence research, programs, and perspectives from more than 20 countries. The primary goal of the conference was to spur the rapid translation of scientific advances into clinical and community practice by strengthening the dialogue between government agencies, treatment providers, and researchers. *For further information, please contact Michael Stirratt at stirrattm@mail.nih.gov.*

The Fifth Annual NIMH-Supported Conference on Pediatric Bipolar Disorder

In March 2007, the NIMH Division of Pediatric Translational Research and Treatment Development (DPTR) held a conference on pediatric bipolar disorder in Bethesda, Maryland. Presentations and discussion focused on a wide range of topics, including gene-environment interactions, utility of non-human animal models, imaging genetics, neuropsychological and neuroimaging approaches, psychopharmacology, and psychosocial functioning. The annual meetings have provided a useful forum for leading investigators to discuss—and for early investigators to receive a thorough grounding on—issues for research on pediatric bipolar disorder. *For more information, please contact Editha Nottelman at enottelm@mail.nih.gov.*

Improving Long-Term Outcomes in ADHD: a Treatment Development Workshop

DPTR and DSIR co-sponsored this workshop in March 2007 to evaluate the current state of knowledge concerning long-term adolescent and adult outcomes in ADHD. The goal of the meeting was to identify research needs and opportunities for advancing treatments to improve long-term functioning. Clinical and basic investigators addressed issues including symptom persistence, the nature of functional impairments in these age groups, predictors of outcome, treatment effects and their current limitations, and neurobiological models and mechanisms, as well as treatment development needs. Discussions included appropriate diagnostic criteria for these older age groups, the need to focus on functional impairments, novel pharmacologic targets, the role of pharmacogenetics in predicting treatment response, approaches for optimizing

and individualizing treatments, and promising novel cognitive and behavioral approaches, as well as future research directions. *For more information, please contact Judith Rumsey at jrumsey@mail.nih.gov.*

2007 Biennial Conference of the Society for Research and Child Development

In March, DPTR and the NIMH Division on Extramural Activities (DEA) joined with the Center for Scientific Review, the National Institute of Child Health and Human Development (NICHD), National Institute on Alcohol Abuse and Alcoholism (NIAAA), and NIDA to participate in several sessions at the biennial conference of the Society for Research and Child Development. The conference, held in Boston, Massachusetts, included several sessions on NIMH research priorities, translational research, mentoring, funding opportunities, policy and review, and ethics of conducting research post-disaster. Conference participants had with the opportunity to meet with NIH program staff individually and in small groups to discuss their research ideas throughout the meeting. *For more information, please contact Courtney Ferrell at cferrell@mail.nih.gov.*

Professional Coalition for Research Progress Annual Meeting

OCRPL convened the third annual Professional Coalition for Research Progress Meeting in Washington, DC in March 2007. The Coalition consists of representatives from professional organizations with an interest in NIMH research. The meeting presented an opportunity for NIMH to share information about research advances, current and new directions for the Institute, and possible future strategies, as well as time for representatives to share their views on NIMH research. *For more information, please contact Alison Bennett at abennet1@mail.nih.gov.*

Brain Awareness Week

NIMH was one of five NIH Institutes to participate in the annual Brain Awareness Week (BAW) health and science information fair held at the National Museum of Health and Medicine in late March 2007. BAW is an international effort occurring annually in March. The Dana Alliance for Brain Initiatives, a nonprofit organization dedicated to increasing public awareness about brain research, organizes the program, which is designed to teach middle school students about the neurosciences and brain health. The National Institute on Aging (NIA), NIAAA, NINDS, and NIDA also participated in the fair. *For more information, please contact Phyllis Quartey at quarteyp@mail.nih.gov.*

The International Congress on Schizophrenia Research Symposium

In March 2007, Dr. Ellen Stover, Director of NIMH's Division of Adult Translational Research and Treatment Development (DATR), chaired the International Congress on Schizophrenia Research in Colorado Springs, Colorado. The symposium brought together the basic neuroscience and clinical science communities to foster the creative acquisition of new knowledge about the disease, and included presentations from Drs. Jeffrey Lieberman, Dan Javitt, David Lewis, and Robert Freedman. *For further information, please contact Ellen Stover at estover@mail.nih.gov.*

Outreach Partnership Program 8th Annual Conference

In April 2007, the NIMH Outreach Partnership Program held its eighth annual conference in Portland, Oregon. The Outreach Partnership Program is a national program that enlists one partner from each of the 50 states and the District of Columbia in conducting outreach and education to help bridge the gap between mental health research and clinical practice. The

conference served as an opportunity for participants to hear scientific updates from Institute staff and guest speakers, to present their own activities, and to network with one another. This year the conference highlighted suicide prevention efforts, anti-stigma education, and the complexities of implementing evidence-based practices. *For more information, please contact Daisy Whittemore at whittemm@mail.nih.gov.*

Partnerships to Integrate Evidence Based Mental Health Practices into Social Work Education and Research Meeting

In April 2007, DSIR and OCRPL hosted this meeting in which participants shared ideas on building and expanding collaborative relationships to support the further integration of research-based mental health practices into social work education. Roundtable discussions provided a venue for participants to brainstorm and provide input, direction, and commitment to “next-steps” for stakeholders. *For more information, please contact Gemma Weiblinger at gweiblin@mail.nih.gov.*

Research on Antisocial Behaviors in Children: Future Directions

In April 2007, DPTR hosted a workshop in Bethesda, Maryland that focused on identifying target areas for new research in the field of disruptive behavior disorders, specifically related to conduct disorder and oppositional defiant disorder. The workshop brought together researchers and NIMH staff in the areas of basic and clinical research to discuss promising research directions and resources necessary to spur scientific advances in understanding the causes and mechanisms underlying disruptive behaviors in children and adolescents. *For more information, please contact LeShawndra Price at lprice@mail.nih.gov.*

Behavioral and Social Sciences Research on HIV/AIDS in the Middle East and North Africa (MENA)

In May 2007, the NIH Office of AIDS Research, NIMH, and the National Institute of Allergy and Infectious Disease (NIAID) sponsored a meeting to promote dialogue on HIV/AIDS in the Middle East and North Africa (MENA), and to outline a research agenda that addresses behavioral and social science priorities for epidemiology and prevention, access to care, and treatment. The meeting, held in Tunis, Tunisia, included scientists, clinical providers, government and policy representatives, and care managers representing seven MENA nations (Algeria, Egypt, Jordan, Lebanon, Libya, Morocco, and Tunisia), as well as U.S. researchers and NIH staff. Formal presentations from both U.S. and MENA representatives were combined with extensive discussion to delineate priority research areas and approaches to establish long term collaborations among MENA nations as well as with U.S. investigators. *For further information, please contact Dianne Rausch at drausch@mail.nih.gov.*

Meeting-based Publications

Following up on the 95th Annual Meeting of the American Psychopathological Association (APPA) held in New York in March 2005, a plenary talk delivered by Richard Nakamura, Deputy Director, NIMH was developed into a book chapter entitled, “Prospects for Prevention of Mental Illness: Integrating Neuroscience and Behavior.” Cheryl A. Boyce, Robert Heinssen, and Courtney Ferrell co-authored the chapter, which describes how basic scientific understandings of mental disorders can be translated into new prevention, intervention, and public policy efforts. The edited volume, *Toward Prevention and Early intervention of Major Mental and Substance Use Disorders*, by former Council member Ming Tsuang, also included chapters on NIH

perspectives from Nora Volkow, Director, NIDA; T.K. Li, Director, NIAAA; and several NIMH grantees who participated in the annual meeting.

Boyce CA, Heinszen R, Ferrell C, Nakamura R. (2007). Prospects for the prevention of mental illness: Integrating neuroscience and behavior. In M Tsuang, WS Stone & MJ Lyons (Eds.), Toward Prevention and Early intervention of Major Mental and Substance Use Disorders. Washington, DC: American Psychiatric Publishing Inc.

The Task Force on Community Preventive Services is an organization of independent, non-Federal members who direct development of the Center for Disease Control and Prevention's *Guide to Community Preventive Services*. Based on systematic reviews of available evidence, the Task Force provides recommendations to public health decision makers on essential community preventive health services. The recently published guide includes strategies for reducing violence by juveniles, a major public health problem in the United States. Eve Moscicki, LaShawndra Price, and Farris Tuma took part in the review which found that transferring juveniles to the adult justice system generally increases, rather than decreases, rates of violence among transferred youth. Overall, the Task Force recommended against laws or policies facilitating the transfer of juveniles from treatment oriented juvenile programs to punitively oriented adult programs. Findings from this review were also published in the supplement to the April 2007 issue of the *American Journal for Preventive Medicine*.

McGowan A, Hahn R, Liberman A, Crosby A, Fullilove M, Johnson R, Moscicki E, Price L, Snyder S, Tuma F, Lowy J, Briss P, Cory S, Stone G; Task Force on Community Preventive Services. Effects on violence of laws and policies facilitating the transfer of juveniles from the juvenile justice system to the adult justice system a systematic review. Am J Prev Med. 2007 Apr;32(4 Suppl):7-28.

Budget

The FY08 President's Budget Request for NIH was submitted to Congress on February 5, 2007. If approved, this request would provide a total NIH program level of \$28.9 billion (See Attachment 1). Highlights of the total NIH request include:

- **NIH Research Project Grants (RPGs):**
The FY08 President's Budget would support an estimated 10,188 competing RPGs at NIH. The President's Budget Request proposes to hold the average cost of competing RPGs at the FY07 level while also allowing no inflationary increases for direct, recurring costs in noncompeting continuation RPGs.
- **NIH National Research Service Award (NRSA) Research Training:**
In the FY08 Request for NIH, stipends for trainees supported by NRSA will remain at FY07 levels. No increases are provided for other components of the NRSA training programs, such as tuition or training related expenses.
- **Intramural Research Program (IRP):**
Funding for the NIH IRP will be decreased by -1.6 percent from the FY07 Joint Resolution.
- **Research Management and Support (RMS)**
RMS funds support the Headquarters and extramural program support activities of each NIH Institute. Funding for the NIH RMS in FY08 will receive an increase of 0.25 percent over the FY07 Joint Resolution.

- **NIH Roadmap for Medical Research:**
In FY08, NIH will direct \$486 million towards Roadmap initiatives. Of this total amount, \$122 million will be provided by the NIH Director's Discretionary Fund (DDF) and the remaining \$364 million will be provided by the ICs.

The FY08 request of \$1.4 billion for NIMH is an increase of \$927 million or +.1 percent over the FY07 Joint Resolution.

- At the FY08 President's Budget level, the NIMH would support an estimated 2,214 total RPGs compared to 2,217 total RPGs in FY07. Approximately 629 of the 2,214 grants to be funded in FY08 will be competing awards, either new or renewal. This compares to an estimated 639 in FY07 and 543 in FY 2006.
- The NIMH success rate for RPGs in FY08 would be about 20 percent compared to an NIH average of about 20 percent.
- The budget will support an estimated 1,340 full-time equivalent NRSA research trainees, equal to the FY07 estimate.
- The FY08 President's Budget Request provides no additional funding toward completion of the John Edward Porter Neuroscience Research Center on the NIH campus.

NIMH actual expenditures by budget mechanism for FY06 and estimates for FY07 Joint Resolution and FY08 President's Budget are displayed on Attachment 2.

Major Awards to NIMH Grantees

In May 2007, the National Academy of Sciences, a private organization of scientists and engineers elected to membership the following NIMH grantees:

- **David J. Anderson, PhD;** investigator, Howard Hughes Medical Institute, and Roger W. Sperry Professor of Biology, California Institute of Technology, Pasadena
- **Ursula Bellugi, EdD;** professor and director, Laboratory of Cognitive Neuroscience, Salk Institute for Biological Studies, La Jolla
- **James S. House, PhD;** Angus Campbell Collegiate Professor of Sociology and Survey Research, Institute for Social Research, University of Michigan, Ann Arbor
- **Eve E. Marder, PhD;** professor of neuroscience, department of biology, Brandeis University, Waltham
- **Michael W. Young, PhD;** vice president of academic affairs and Richard and Jeanne Fisher Professor, The Rockefeller University, New York City

Staff Changes

Arriving:

LaKiesha Adu joined the Office of Science Policy, Planning, and Communications (OSPPC) in April as an Administrative Assistant. She is experienced in making travel arrangements, working

in QVR, and proofreading and will be assisting the Office with many other activities as well. Before joining OSPPC, she served as a Program Support Specialist at NINDS.

Dianna Bailey, a senior specialist, joined the DEA Grants Management Branch in March. Ms. Bailey came to NIMH after three years at the Agency for Healthcare Research & Quality. Prior to that, she had been a 30-year NIH employee, most recently as a grants specialist at NICHD.

Victoria Carper, MPA, in April became Team Leader in the Grants Management Branch in DEA. She rejoins NIH after a hiatus to assist a small non-profit organization create a grants department. A 19-year veteran of NIH, Ms. Carper previously served at NIAID and the Office of Policy for Extramural Research Administration (OPERA), and in 2000 was appointed the first Chief Grants Management Officer for the National Center for Complimentary and Alternative Medicine (NCCAM).

Vinod Charles, PhD, accepted a position as a Scientific Review Administrator with the Scientific Review Branch of the NIMH DEA. Prior to joining the Institute, Dr. Charles served as an SRA within the Brain Disorders and Clinical Neurosciences Branch of the Center for Scientific Review. He has also held positions at the National Human Genome Research Institute, first as an Intramural Research Training Award (IRTA) Postdoctoral Fellow and then Pharmacology Research Associate (PRAT) Fellow, and as Research Scientist and Program Manager for Psychiatric Genomics, Inc., where he led the *in vivo* biology group for drug discovery and target validation. The primary focus of this group was the investigation of gene dysregulation in schizophrenia, bipolar disorders, major depression and autism. Dr. Charles received his doctoral degree in 1998 from Rush University.

Thomas Lehner, PhD, MPH, was selected in February as Chief of the Genomics Research Branch in DNBBS after a competitive search. Dr. Lehner joined NIMH as a program officer in the Office of Human Genetics and Genomic Resources in 2004 and has been Acting Director of the Office since April 2005. He trained in statistical genetics and genetic epidemiology at the University of Vienna, Austria, and Columbia University in New York City. Before joining NIMH, Dr. Lehner held an academic position at The Rockefeller University in New York City and was in charge of developing research programs at a large biotechnology company in Boston.

Megan Libbey, PhD, accepted a position as Scientific Review Administrator in the DEA Scientific Review Branch. She received her undergraduate degree from Wellesley College, and later joined the laboratory of Dr. Jacqueline Crawley as a pre-doctoral fellow. She then enrolled in the Neuroscience program at Boston University where she received her PhD under the tutelage of Dr. Howard Eichenbaum. Following a post-doctoral fellowship in the laboratory of Dr. Serge Laroche, Dr. Libbey was employed by Ogilvy Healthworld in Paris, France, where she was responsible for the development and creation of deliverables in pan-European campaigns for top-ten pharmaceutical companies.

A. Roger Little, PhD, joined OSPPC full-time in March as the Senior Advisor for Scientific Coordination, which includes serving as the NIMH Liaison for Roadmap and Blueprint activities. Dr. Little previously served in this position as a part-time detail from the Extramural Review Branch where he was an SRA for two years. From 1998-2004, he conducted research at

CDC's National Institute for Occupational Safety and Health in Morgantown, West Virginia to identify the underlying neural signaling pathways involved in the brain injury response.

Robert Mays, PhD, will be assuming the majority of duties previously assigned to Mr. Sherman Ragland, and has accepted the position of Acting Chief, Mental Health Disparities Program. He will be responsible for the reports to Congress, including reports on Historically Black Colleges and Universities, Hispanic Serving Institutions, and Tribal Colleges. Dr. Mays has also assumed leadership, as Chair of the Mental Health Disparities Team, and will take on several new initiatives as well.

Molly Oliveri, PhD, in April 2007 was selected as Director of DPTR after a competitive search. Dr. Oliveri's career with NIMH spans two decades, starting in 1987 when she joined the Institute as Chief of the Personality and Emotion Program. Since then she has held a variety of increasing responsibilities, including Chief of the Behavioral Science Research Branch, Deputy Division Director of DPTR, and, most recently, Acting Director of DPTR. Prior to joining NIMH, Dr. Oliveri was a faculty member of the Department of Psychiatry and Behavioral Sciences at the George Washington University School of Medicine from 1975-87.

Ana Velez joined the NIMH management team in February as the new NIMH Budget Officer. Ms. Velez previously served as the Budget Officer for the National Center for Minority Health and Health Disparities (NCMHD) for the last several years. She has been a part of the NIH Community since 1997, serving in various roles ranging from NIH Presidential Management Fellow to Senior Budget Analyst at National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

Tracy Waldeck, PhD, joined the DEA Office for Special Projects in March as the Assistant Director for Special Projects. Dr. Waldeck earned her doctoral degree in clinical psychology from the University of Georgia in 1999 and then completed post-doctoral training at Johns Hopkins School of Medicine. She first came to NIMH in 2002, working at the Intramural Research Program in the Mood and Anxiety Disorders Program under Dr. Dennis Charney and later Dr. Hussein Manji. Dr. Waldeck joined the extramural community in 2005 as a Scientific Review Administrator.

Departing:

Mary Farmer, MD, left NIMH in April 2007 following 27 years of service to the government to spend more time with her family.

Sherman (Sherm) Ragland, MSW, retired from Federal service in February 2007, after his distinguished career serving the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA)—precursor to SAMHSA—and NIMH since 1975.

Takisha Schulerbrandt, PhD, MPH, left the NIMH Reports and Analysis Branch of OSPPC in April to pursue a position with IMC, Inc.