DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

NATIONAL ADVISORY COUNCIL FOR BIOMEDICAL IMAGING AND BIOENGINEERING

Summary of Meeting[1]
May 17, 2013

The National Advisory Council for Biomedical Imaging and Bioengineering (NACBIB) was convened for its 32nd meeting on May 17, 2013, at the Bolger Center in Potomac, Maryland. Dr. Roderic I. Pettigrew, Director of the National Institute of Biomedical Imaging and Bioengineering (NIBIB), presided as Council chairperson. In accordance with Public Law 92-463, the meeting was open to the public from 9:00 a.m. to 11:30 a.m. for review and discussion of program development, needs, and policy. The meeting was closed to the public from 12:40 p.m. to 1:15 p.m. for consideration of grant applications.

Council members present:
Dr. W. Eric L. Grimson, Massachusetts Institute of Technology, Cambridge, MA
Dr. Nola M. Hylton, University of California, San Francisco, CA
Dr. Cato T. Laurencin, University of Connecticut, Farmington, CT
Dr. Mark Musen, Stanford University, Stanford, CA
Dr. Buddy Ratner, University of Washington, Seattle, WA
Dr. Bruce Tromberg, University of California, Irvine, CA
Dr. Michael Yaszemski, Mayo Clinic College of Medicine, Rochester, MN

Ex officio members present:
Dr. P. Hunter Peckham, U.S. Department of Veterans Affairs, Cleveland, OH
Dr. Sohi Rastegar, National Science Foundation, Arlington, VA

Council members absent:
Dr. John C. Gore, Vanderbilt University, Nashville, TN
Dr. Hedvig Hricak, Memorial Sloan Kettering Cancer Center, New York, NY
Dr. Etta D. Pisano, Medical University of South Carolina, Charleston, SC
Dr. Sheldon Weinbaum, The City College of New York, New York, NY

Ex officio members absent:
Dr. Francis Collins, National Institutes of Health, Bethesda, MD
Dr. Anne Plant, National Institute of Standards and Technology, Gaithersburg, MD
Ms. Kathleen Sebelius, U.S. Department of Health and Human Services, Washington, DC
Dr. James G. Smirniotopoulos, Uniformed Services University of the Health Sciences, Bethesda, MD

Chairperson:
Dr. Roderic I. Pettigrew

Executive Secretary:
Dr. Anthony Demsey

[1] For the record, it is noted that members absent themselves from the meeting when the Council is discussing applications (a) from their respective institutions or (b) in which a conflict of interest may occur. This procedure only applies to applications that are discussed individually, not to "en bloc" actions.

Also present:
NIBIB staff present for portions of the meeting:

Mr. Angelos Bacas
Dr. Richard A. Baird
Ms. Barbara Cantilena
Ms. Shirley Coney-Johnson
Dr. Richard Conroy
Ms. Zoe Ann Copeland
Ms. Nancy Curling
Mr. Jeff Domanski
Mr. Anthony Dorion
Dr. Henry Eden
Ms. Kate Egan
Ms. Angela Eldridge
Ms. Kathryn Ellis
Dr. Zeynep Erim
Dr. David George
Ms. Marie Gill
Ms. Pam Glikman
Dr. Ruth Grossman
Dr. John Hayes
Ms. Eunica Haynes
Dr. William Heetderks
Dr. Rosemarie Hunziker
Dr. Chris Kelley
Ms. Margot Kern
Dr. Brenda Korte
Dr. Steven Krosnick
Dr. Richard Leapman
Ms. Karin Lee
Dr. Christina Liu
Dr. Guoying Liu
Dr. Hector Lopez
Dr. Xiao-Zhong (James) Luo
Dr. Shadi Mamaghani
Dr. Alan McLaughlin
Ms. Jessica Meade
Mr. Todd Merchak
Mr. Joe Mosimann
Dr. Peter Moy
Dr. Vinay Pai
Dr. Grace Peng
Dr. Karen Peterson
Ms. Vicki Rein
Ms. Christine Rogers
Mr. Rolando Romero
Ms. Stephanie Sabourin
Dr. Antonio Sastre
Dr. Belinda P. Seto
Mr. Shaun Sims
Dr. Manana Sukhareva
Ms. Florence Turska
Ms. Keisha Whitaker-Duncan
Dr. Ruixia Zhou
Dr. Steven Zullo

Non-NIBIB National Institutes of Health (NIH) employees:
Dr. Robert Elliott, CSR

Non-NIH Federal employees:
None

Members of the public present for portions of the meeting:
Ms. Taryn Gnip, NOVA Research Company
Mr. Damon Kelly, Bolger Center
Mr. Joshua Narotsky, National Capitol Captioning, LLC
Mr. Michael Peters, American College of Radiology

I. Call to Order: Dr. Anthony Demsey

Dr. Anthony Demsey called to order the 32nd meeting of the National Advisory Council for Biomedical Imaging and Bioengineering. He reminded attendees that the morning session of the meeting was open to the public, welcomed attendees, and introduced Dr. Roderic Pettigrew, who formally welcomed all participants.

II. Director's Remarks: Dr. Roderic I. Pettigrew

A. Outgoing Council Members

Dr. Pettigrew thanked Drs. Hedvig Hricak and Buddy Ratner for their service to the Council. He noted that this would be their last meeting, since their terms of appointment end on August 31, 2013.

B. In Memoriam

Dr. Pettigrew recognized the recent passing of Ms. Carol Fitzpatrick, who had spent the last seven years as Committee Management Officer of NIBIB. She was deeply involved with the planning and organizing of NACBIB meetings. NIBIB will name one of its conference rooms in Ms. Fitzpatrick's honor.

C. Awards

Dr. Pettigrew described several grantee awards of note. Council member Dr. Michael Yaszemski received the 2013 Tipton Leadership Award from the American Academy of Orthopedic Surgeons in recognition of his orthopaedic research and mentoring activities. NIBIB grantees Drs. Chien Ho and Mitchell Schnall were recognized with 2013 Gold Medals from the International Society for Magnetic Resonance in Medicine. Three grantees received 2013 Institute of Electrical and Electronics Engineers (IEEE) in Medicine and Biology awards: Dr. Theodore Berger received the Academic Career Achievement Award; Dr. Muhammad Hamid Zaman received the Early Career Achievement Award; and Dr. Ali Khademhosseini received the Technical Achievement Award.

D. NIH FY13 Budget and Legislation

The government is operating on a full-year Continuing Resolution (CR) for fiscal year (FY) 2013. The budget decreased by 5.7 percent due to sequestration.

During FY2013, NIBIB has received 133 grant applications scoring within the 10th percentile, compared with 73 grant applications scoring at this level in FY2009. In order to deal with the increased number of excellent grant applications and decreased funding levels, NIBIB has set the R01/R21 payline at the 9th percentile for repeat and established investigators. All noncompeting research project grants and Centers will be cut by 5.7 percent.

E. NIH Activities Update

Coordination of STEM Programs

Over the past ten years, a number of reports have expressed concern over the large number of Federal Science, Technology, Engineering, and Mathematics (STEM) education programs, and has subsequently recommended better coordination between agencies. The President's FY2014 Budget proposed the reorganization of Federal STEM education programs to focus resources at the Department of Education, the National Science Foundation (NSF), and the Smithsonian. Nine NIH programs are being transferred: six programs aimed at education and training at the K-12 level and three at the post-undergraduate level.

BRAIN Initiative

President Obama announced the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative on April 2. The goal of the initiative is to map the function of all neurons to revolutionize understanding, treatment, and prevention of brain disorders. The President's FY2014 Budget requests approximately $100 million from NIH, the Defense Advanced Research Projects Agency (DARPA), and NSF to support this effort. Dr. Collins established the BRAIN Working Group of the Advisory Committee to the Director, comprising 15 leading neuroscientists, to lead the initiative. Three members of the BRAIN Working Group are NIBIB grantees: Drs. Mark Schnitzer, Roger Tsien, and Kamil Ugurbil.

Dr. Pettigrew highlighted the work of Dr. Schnitzer, who has developed a pulsed laser microendoscope that successfully recorded about 1,200 hippocampal neurons in a freely behaving mouse. Video of the behaving mouse shows that the neuron firing pattern correlated with the spatial position of the mouse within one body length. Dr. Pettigrew also shared a link to a hand-controlled software for navigating 3-D images (http://www.oblong.com/blog/posts/oblong-at-ome/). This brain visualization tool attempts to demonstrate the potential of data exploration, visualization, interaction, and analysis for precision medicine.

Take Your Child to Work Day

NIBIB participated in Take Your Child to Work Day on April 25, with a tremendous reception by both K-12 students and parents. Dr. Pettigrew acknowledged the team in charge of planning the day. A summary of NIBIB's activities will be featured in the *NIH Record*.

F. NIBIB Activities Update

Conferences Under Development

The Molecular Imaging Phase III conference is a followup to the initial "Roadmap" initiative, which was aimed at imaging single molecular events. NIBIB seeks Council input to identify compelling opportunities in this research area and to help design an initiative that capitalizes on those opportunities. NIBIB also is planning a new Annual Joint NIBIB-National Cancer Institute (NCI) Conference on Cancer Technologies. The first conference is scheduled for Fall 2013. NIBIB requests Council input on identifying the most compelling opportunities in the field of cancer technologies and how to plan the conference in order to best advance this research area.

Updated Website

A new NIBIB website will be released soon. The new website is based on a digital communications platform used by the White House and will have increased content for both the public and grantees.

G. Science Highlights

Biomaterial-based Cartilage Repair

Dr. Jennifer Elisseeff at Johns Hopkins University has developed a biomaterial-based cartilage repair approach that augments microfracture treatment for cartilage replacement. The adhesive hydrogel technology, which was previously shown to restore tissue in goats, is now being tested in humans. The first clinical study results reveal higher levels of tissue fill, less pain, and equivalent or improved knee function as exhibited with real-time magnetic resonance imaging (MRI).

Mouse MRI to Discover the Functional Roles of Genes, Receptors, and Enzymes

Dr. Frederick Epstein at the University of Virginia is developing MRI techniques for assessing the structure, function, and perfusion of the cardiovascular system, particularly in the setting of cardiovascular disease. MRI makes it possible to assess organ and tissue function in a noninvasive way. One of these techniques is Cine DENSE (Displacement Encoding with Stimulated Echoes) MRI, which is being used to visualize cardiovascular displacement and strain in gene-modified mice. This technology has enabled researchers to identify the gene that codes for the enzyme responsible for the contractile function of the heart.

Discussion

Dr. Pettigrew asked about the clinical utility of biomaterial-based cartilage repair.

Dr. Yaszemski said that microfracture can sometimes be successful but will not result in long-lasting repair of the cartilage defect. Patients with focal cartilage defects are typically young and will develop generalized arthritis while they are still young. He stated that Dr. Elisseeff's technology is a good advance for this field.

Dr. Laurencin added that large-scale clinical trials are needed to demonstrate efficacy of this new technology. Some technologies work well in animals, but scaling those technologies up for use in large-scale human trials is difficult. This technology could be successful for cartilage repair, but much work is needed to develop the next generation of arthritis treatment strategies.

III. Review of Council Procedures and Regulations: Dr. Anthony Demsey

Dr. Demsey noted for the record that a quorum was present for this Council meeting. Council members Drs. Hedvig Hricak, Etta Pisano, and Sheldon Weinbaum were unable to attend. *Ex officio* members Drs. Anne Plant and James Smirniotopoulos were also unable to attend. Dr. Demsey welcomed visitors and members of the science press and scientific society constituencies. He thanked Ms. Pam Glikman for planning the meeting.

A. Council Regulations, Policies, and Procedures

Dr. Demsey summarized elements of the Government in the Sunshine Act and the Federal Advisory Committee Act that govern all Advisory Council meetings. These acts require the U.S. Department of Health and Human Services to open Advisory Council meetings to the public except when proprietary or personal information is discussed. To comply with these regulations, NACBIB meetings are open to the public for all except the review of individual grant applications. Dr. Demsey reviewed conflict-of-interest, confidentiality, and lobbying guidelines.

B. Future NACBIB Meeting Dates

The next NACBIB meeting is scheduled for Thursday, September 12, 2013. Dr. Demsey asked Council members to inform him about conflicts with any of the upcoming meeting dates listed at the bottom of the agenda.

C. Approval of the January 25, 2013, NACBIB Meeting Minutes

A motion to approve minutes of the January 25, 2013, NACBIB meeting was forwarded, seconded, and approved unanimously.

IV. Brain Imaging and Genomics in 26,000 People—The ENIGMA Project: Dr. Paul Thompson

Dr. Vinay Pai, NIBIB, introduced Dr. Paul M. Thompson, professor of Neurology and Psychiatry at the University of California, Los Angeles, School of Medicine. Dr. Thompson presented the work of the ENIGMA (Enhancing Neuro Imaging Genetics Through Meta-Analysis) project.

ENIGMA is the largest brain imaging study in the world. A worldwide consortium comprising 125 institutions and 207 co-authors and principal investigators, ENIGMA is a massive global collaboration that enables researchers in imaging genomics to conduct studies to understand brain structure and function, based on computed tomography (CT), MRI, diffusion tensor imaging (DTI), functional MRI (fMRI) and genome-wide association scan (GWAS) data. The consortium pools human brain images and genome-wide scans to discover variants that affect the brain and disease risk. To date, over 26,000 subjects have been scanned. This vast sample has enabled researchers to see how single-letter changes in DNA affect the brain, in the midst of all other factors that affect the brain (i.e., age, sex, education, abused drugs, alcohol, body mass index). Epidemiologic analyses on exercise, diet, medication, etc., also can be conducted with the images. The goal is to discover genes that damage the brain, affect brain wiring, and cause disease, and to estimate personal risk for disease. The ability to estimate personal risk can boost the power of drug trials by enrolling patients who are most likely to decline.

ENIGMA collects a number of data types relevant to understanding brain disease, ranging from structural MRI and CT scans to functional and metabolic imaging analyses and optical imaging. P41 funding from NIBIB enabled ENIGMA to collaborate with experts around the world who collect longitudinal MRI data. Dr. Thompson presented a video of the brain that was reconstructed from a cohort of patients with Alzheimer disease. The video showed the thinning of the grey matter over a period of two years. These videos can be compiled for a host of disorders and have practical use in drug trials. For example, imaging data were compiled to show the rate of brain tissue loss in schizophrenia patients taking two different antipsychotic drugs. Patients receiving Haldol lost tissue at a much faster rate than patients receiving the newer drug, Olanzapine. Similarly, computational methods were used to plot the growth rate of the brain based on serial MRI scans of children taken every 2 years for the past 15 years.

Many lifestyle factors affect the brain, including drug abuse. The pattern of brain tissue loss of frequent methamphetamine users is similar to the brain loss patterns of patients with Alzheimer disease. Cardiovascular studies with imaging components have shown that people who exercise more have slower brain loss; exercise protects the brain more than any Alzheimer medication. On the other hand, stress and cortisol increase tissue loss. A recent study revealed that vitamin B supplementation slows the rate of brain atrophy in the elderly. Obesity is one of the best predictors of brain tissue loss. People with a higher body mass index tend to have more brain atrophy at baseline and a faster rate of tissue loss. Geneticists discovered

an "obesity gene" (*FTO*) and ENIGMA researchers were able to demonstrate the gene's effects in brain images.

Brain imaging can help elucidate the findings of geneticists. Three Alzheimer disease risk genes were discovered three years ago by screening the genome and searching for single nucleotide polymorphisms (SNPs) that were overrepresented in Alzheimer patients versus controls. Geneticists did not know what role one of the genes, "Cluster N" or "*CLU*," had on the brain. DTI was conducted on patients with the gene and controls. The images revealed that Alzheimer patients with the *CLU* gene had poorer brain integrity a full 50 years before the disease typically hits. This effect is even stronger for carriers of a schizophrenia risk gene variant. With the help of engineers, ENIGMA researchers were able to develop a polygenic test for common gene variants to predict brain integrity and rate of brain loss. The recently discovered gene *TREM2*, which is carried by 1 percent of the population, doubles the rate of brain tissue loss and doubles the risk for Alzheimer disease. The polygenic test, and particularly the identification of the *TREM2* gene, is useful for drug trial enrichment, as trials could enroll patients who are likely to decline faster.

ENIGMA was created to identify predictors of brain health. Algorithms were developed and sent to all 125 participating ENIGMA institutions to identify relationships between genetic variants or brain measures (biomarkers) and health factors. ENIGMA members compute brain measures from scans, test associations between brain measures and over 1 million SNPs, and conduct meta-analyses by combining brain effects across sites. Each site's "vote" depends on its sample size. Ensuring that effects are reproducible boosts the power to identify effects that no site could identify on its own. The online ENIGMA-Vis Tool enables researchers to look up genes and see what effect they have on the brain. This tool has helped numerous genetics projects that are not using imaging.

ENIGMA working groups focus on particular disorders and diseases, such as schizophrenia, bipolar disorder, and major depression. These working groups have enabled worldwide meta-analysis of data relevant to specific disorders and diseases. ENIGMA has access to over 1,600 brain scans from schizophrenia patients; these scans were compared in an effort to identify a brain biomarker for the disease.

Comparing data from ENIGMA sites across the globe also permits the identification of patterns of medication use and its effects on the brain. Tissue loss maps of people who have taken different drugs can be created to identify population distinctions between patterns of tissue loss and different kinds of therapy.

Dr. Thompson highlighted two projects that are complementing the work of ENIGMA. The Human Connectome Project (HCP) is a project to construct a map of the complete structural and functional neural connections *in vivo* within and across individuals. The HCP represents the first large-scale attempt to collect and share data of a scope and detail sufficient to begin the process of addressing deeply fundamental questions about human connectional anatomy and variation. One of Dr. Thompson's postdoctoral fellows, Dr. Neda Jahanshad, suggested screening the connectome for genetic variants that affect the density of connections between different parts of the brain. In order to do this, Dr. Jahanshad developed an approach for prioritizing connections in order of their heritability. By scanning the human connectome with a selected set of criteria, she found a gene that Dr. Robert Green (Harvard University) subsequently identified to be an Alzheimer disease risk gene.

The Evolving Partitions to Improve Connectomes (EPIC) project randomly segments the cortex into 500 regions and examines the connections between the regions. The connection matrix is plugged into a classifier that distinguishes patients and controls and then requires continued adjustment. EPIC was 81 percent accurate for detecting Alzheimer disease based on connectivity patterns alone. This approach requires further refinement, yet exhibits the advances that can be brought by mathematicians and engineers to the field of neuroimaging.

In the future, the field of neuroimaging may become much more collaborative. As budgets shrink, there is more incentive for researchers to collaborate and draw upon previously funded data collections. Neuroimaging researchers are starting to realize the ultimate benefits of data sharing.

Dr. Thompson closed his presentation by acknowledging the funding support of NIBIB, which has enabled much of the research he presented today.

Questions and Discussion

Dr. Grimson asked how ENIGMA tries to guarantee the quality of brain measures studied. Dr. Thompson replied that no single person can survey the quality of the aggregated data that ENIGMA supports. ENIGMA institutions must run their scans through certain metrics and norms to ensure accuracy. The use of standard algorithms and a second phase of screening to identify true outliers ensures some level of data quality. Additionally, the fact that ENIGMA data are public and very visible increases the likelihood that errors will be caught.

Dr. Hylton questioned whether there are any automated methods for controlling for data differences. Dr. Thompson answered that member sites use different scanners to image patients. Acknowledging that different scanners are used and looking at whether that has any bearing on results would strengthen ENIGMA's data set.

Dr. Ratner asked about the correlation between enlarged ventricles and mental illness. Dr. Thompson responded that ventricle enlargement is a biomarker with a somewhat uncertain relationship with neurobiology. It is thought that the ventricles enlarge as a result of any type of brain tissue loss—it is a nonspecific relationship. That said, generally, enlarged ventricles are a good measure of Alzheimer disease progression.

Dr. Seto wondered whether any of the collaborating ENIGMA sites are looking at mechanisms beyond the genome-wide association scan. Dr. Thompson said that the Cluster-C (*CLU-C*) gene has been studied for a while, and parallel tracks in science enable the discovery of gene functions. Dr. Thompson confirmed that the *CLU-C* gene is being studied in twin studies.

Dr. Rastegar asked for further clarification on the studies of nondrug effects (i.e., exercise and vitamin supplementation). Dr. Thompson reported that a paper on the protective factors of vitamin B supplementation will be published in *PNAS*. ENIGMA also found an effect of vitamin B on the brain, but the evidence was not as strong.

Dr. Pettigrew wondered about the differences in brain thickness as a consequence of medications used in the treatment of schizophrenia. He asked if anyone has looked at mechanisms of action of Haldon versus Olanzapine. Dr. Thompson replied that he consulted Dr. Judy Rapoport at the National Institute of Mental Health on this issue. The older drug, Haldon, affects dopamine receptors; whereas, the newer drug is a neuromodulator of serotonin and histamine. Olanzapine has a broader pharmacological profile and tends to keep brain function in more equilibrium than does Haldon, which blocks an entire system crucial to the brain. Dr. Thompson also stated that Olanzapine has a more reasonable side effect profile than does Haldon, but it does contribute to obesity.

V. Adjournment

The open session of the NACBIB meeting was adjourned at 11:30 a.m.

VI. Closed Session

The grant application review portion of the meeting was closed to the public in accordance with provisions set forth in Section 552b(c)(4) and 552b(c)(6), Title 5, U.S. Code, and 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. appendix 2). The closed session was adjourned at 1:15 p.m.

Certification:

We certify that, to the best of our knowledge, the foregoing minutes are accurate and complete.[2]

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Anthony Demsey, Ph.D.
Executive Secretary,
National Advisory Council for Biomedical Imaging and Bioengineering
Director,
Office of Research Administration
National Institute of Biomedical Imaging and Bioengineering

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Roderic I. Pettigrew, Ph.D., M.D.
Chairperson,
National Advisory Council for Biomedical Imaging and Bioengineering
Director,
National Institute of Biomedical Imaging and Bioengineering

[2] These minutes will be approved formally by the Council at the next meeting on September 12, 2013, and corrections or notations will be stated in the minutes of that meeting.