Mapping Awake Brain Activity

In a paper e-published on April 10 ahead of print in the *Journal of Neuroscience*, scientists at the U.S. Department of Energy Brookhaven National Laboratory (BNL) and collaborators detailed the development of a new way to use light and chemistry to map brain activity in fully awake, moving animals. The technique employs light-activated proteins to stimulate targeted brain cells and PET imaging to trace the effects of site-specific stimulation throughout the entire brain. The method will allow researchers to map exactly which downstream neurologic pathways are activated or deactivated by stimulation of targeted brain regions and how that brain activity correlates with specific behaviors and/or disease conditions.

"This technique gives us a new way to look at the function of specific brain cells and map which brain circuits are active in a wide range of neuropsychiatric diseases—from depression to Parkinson disease, neurodegenerative disorders, and drug addiction—and also to monitor the effects of various treatments," said the paper's lead author, Panayotis (Peter) Thanos, PhD, a neuroscientist and director of the Behavioral Neuropharmacology and Neuroimaging Section, part of the National Institute on Alcohol Abuse and Alcoholism Laboratory of Neuroimaging at BNL, and a professor at Stony Brook University (NY). "Because the animals are awake and able to move during stimulation, we can also directly study how their behavior correlates with brain activity."

The new brain mapping method combines recent advances in optogenetics with previous BNL work and the laboratory's history of research on PET imaging agents. The researchers modified a virus to deliver a light-sensitive protein to specific brain cells in rats. After stimulating those proteins with light through an optical fiber, they monitored overall brain activity with ^{18}FDG PET. Coregistration with MR allows voxel mapping that, in effect, opens the entire awake brain to exploration. "If we want to know more about the role played by specific types of receptors—say the dopamine D1 or D2 receptors involved in processing reward," said Thanos. "We could tailor the light-sensitive protein probe to specifically stimulate one or the other to tease out those effects."

Brookhaven National Laboratory

^{188}Re-Labeled Bacteria and Pancreatic Cancer

Researchers at Albert Einstein College of Medicine of Yeshiva University (New York, NY) announced on April 22 the development of a therapy for pancreatic cancer using *Listeria* bacteria to selectively infect and deliver radioisotopes into tumor cells. The experimental treatment significantly decreased the number of metastases in a mouse model of highly aggressive pancreatic cancer without harming healthy tissue. The study was published in the April 22 online edition of the *Proceedings of the National Academy of Sciences*.

"We're encouraged that we've been able to achieve a 90% reduction in metastases in our first round of experiments," said coauthor Claudia Gravekamp, PhD, associate professor of microbiology and immunology at Einstein. "With further improvements, our approach has the potential to start a new era in the treatment of metastatic pancreatic cancer."

The group had previously noted that an attenuated form of *Listeria* monocytogene (*Listeria*^{at}) can infect cancer cells but not normal cells, because the tumor microenvironment suppresses the normal immune response. Ekaterina Dadachova, PhD, a professor of radiology and microbiology and immunology at Einstein, worked with Gravekamp and others to radiolabel *Listeria*^{at} with ^{188}Rh.

Mice with metastatic pancreatic cancer were given intraabdominal injections of the radiolabeled *Listeria*^{at} once a day for 7 d, followed by a 7-d rest and 4 additional daily injections. After 21 d, the treatment had reduced the metastases by 90% compared with untreated controls. The agent concentrated in metastases and to a lesser extent in primary tumors but not in healthy tissues, with no adverse effects noted. In a press release from Einstein, the authors noted the potential for even greater efficacy. "We stopped the experiment at 21 d because that's when the control mice start dying," said Dadachova. "Our next step is to assess whether the treatment affects the animals' survival." The authors added that the treatment might be improved by fine-tuning the treatment schedule, using higher doses of radiation, or piggybacking additional anticancer agents onto the bacteria. Einstein has filed a patent application related to this research that is currently available for licensing to partners interested in further developing and commercializing this technology.

Albert Einstein College of Medicine

Global Overview of Hybrid Imaging

In September 2012 the International Atomic Energy Agency (IAEA) held a meeting in Vienna, Austria, to address the international status of hybrid imaging, with a focus on worldwide challenges and opportunities for the developing world. The results of the meeting were summarized in an article in the May issue of *Seminars in Nuclear Medicine* (2013;43:208–223). Kashyan et al. looked in depth at PET/CT and SPECT/CT growth and provided separate summaries and discussions of education and training as well as current technology status in global regions.

They noted that, in general, nuclear medicine "provides useful inputs in management of chronic and noncommunicable diseases" and that "as these disease burdens are increasing worldwide, there is a converging need for an increase in nuclear medicine

practice across the developing and developed world." However, current growth is challenged by disparities in access, education, and perceived value of the relevant tools. The authors identified the main strengths of current IAEA activities in hybrid imaging as a strong existing network, the potential for further partnerships, an awareness of regional social and cultural barriers, and good identification of appropriate niche areas for growth. Weaknesses were identified as limited resources and disparities in use of technology driven by market forces. One opportunity identified was that of concerted efforts to apply hybrid technologies in noncommunicable diseases. The IAEA action plan will involve helping member states to improve the use of hybrid imaging and to address and deal with heterogeneities in education, access, and perceived value of the technology within diverse health care systems.

Seminars in Nuclear Medicine

Next-Generation AD Model

In an article appearing in the April 10 issue of the *Journal of Neuroscience* (2013;33:6245–6256), a consortium of researchers sponsored in part by the National Institute of Neurological Disorders and Stroke (NINDS) reported on the development of a transgenic rat model (line TgF344-AD) with the full array of brain changes associated with Alzheimer disease (AD). The Tg rat model expresses mutant human amyloid precursor protein and presenilin 1, each independent causes of early-onset familial AD. The rats manifest the age-dependent cerebral amyloidosis that precedes tauopathy, gliosis, apoptotic loss of neurons in the cerebral cortex and hippocampus, and cognitive disturbance, demonstrating progressive neurodegeneration of the Alzheimer type.

Previous studies with transgenic mice and rats that have the APP and presenilin 1 mutations only partially reproduced the problems caused by AD. The animals had memory problems and many amyloid-β plaques but none of the other disease hallmarks, such as neurofibrillary tangles and neuron loss. "This new rat model more closely represents the brain changes that take place in humans with AD, including tau pathology and extensive neuronal cell death," said Roderick Corriveau, PhD, a program director at NINDS. "The model will help advance our understanding of the various disease pathways involved in AD onset and progression and assist us in testing promising interventions." An April 9 press release from NINDS discussed the promise of the model in advanced translational research.

Verification experiments were conducted to confirm the presence of neurofibrillary tangles. Additional experiments showed that about 30% of neurons in affected regions died with age, the largest amount of cell death seen in an AD rodent model, and that some glial cells acquired shapes reminiscent of the activated glia found in patients. Activation of glia occurred earlier than amyloid plaque formation, which suggests the identification of an early degenerative event and new treatment target that scientists studying other rodent models may have missed. "We believe the rats will be an excellent, stringent preclinical model for testing experimental AD therapeutics," said Terrence Town, PhD, the study's senior author and a professor at the University of Southern California Keck School of Medicine (Los Angeles).

Journal of Neuroscience
National Institute of Neurological Disorders and Stroke

CMS MPPR Policy Critiqued

In an article e-published on April 9 in the *Journal of the American College of Radiology*, Richard Duszak, Jr., MD, from the Harvey L. Neiman Health Policy Institute (Reston, VA), and colleagues looked at the accuracy of current Centers for Medicare & Medicaid Services (CMS) multiple procedure payment reduction (MPPR) policies in quantifying potential physician work efficiencies and appropriate MPPRs for different same-session diagnostic imaging studies interpreted by different physicians in the same group practice. The group analyzed data from the Medicare Resource-Based Relative Value Scale to identify the contributions of various preservice, intraservice, and postservice physician diagnostic imaging work activities. An expert panel looked at potential duplications in professional work activities, and maximum potential duplications for various imaging modalities were calculated and compared with CMS payment policy supporting data. The authors found no potential intraservice work duplication when different examination interpretations were made by different physicians in the same group practice. When multiple interpretations in the same modality were made by different physicians, maximum calculated potential duplicate pre- and postservice activities ranged from 5% (for radiography, fluoroscopy, and nuclear medicine) to 13.6% (for CT). This was estimated to result in overall potential total work reductions ranging form 1.39% (for nuclear medicine) to 2.73% (for CT).

The authors concluded that "although potential efficiencies exist in physician preservice and postservice work when same-session, same-modality imaging services are rendered by different physicians in the same group practice, these are relatively minuscule and have been grossly overestimated by current CMS payment policy." They called for "greater transparency and methodologic rigor in government payment policy development."

Journal of the American College of Radiology

U.S. Dementia Costs Rise

The costs of caring for people with dementia in the United States in 2010 were between $159 and $215 billion, and those costs could rise dramatically with the increase in numbers of older people in coming decades, according to estimates by researchers at the RAND Corporation (Santa Monica,

CA) and the University of Michigan (Ann Arbor). These costs of care are comparable to and possibly greater than those for heart disease and cancer. The study, supported by the National Institutes of Health (NIH) and published April 4 in *The New England Journal of Medicine*, calculated direct medical expenditures and costs attributable to the large network of informal, unpaid care that supports people with dementia.

The researchers first looked at care purchased in the health care market, including formal costs for nursing homes, Medicare, and out-of-pocket expenses. These were estimated to be $109 billion in 2010, exceeding direct health costs for heart disease ($102 billion) and cancer ($77 billion) that year. Adding informal, unpaid care to the equation as much as doubled the estimated total national costs. The study estimated full costs per case of dementia in 2010 at $41,000 to $56,000. The lower number accounts for unpaid wages among caregivers, and the higher figure valued hours of informal care as the equivalent of formal paid care. The range of national expenditures was based on an estimated prevalence of dementia of 14.7% in the U.S. population older than 70 y.

The researchers also projected rapidly escalating costs as the baby boom generation grows older. The population aged ≥65 y will double to about 72 million over the next 20 y, and national health expenditures for dementia could come close to doubling by 2040. "These findings reveal that the enormous emotional and physical demands of caring for people with dementia are accompanied by the similarly imposing financial burdens of dementia care," said Richard J. Hodes, MD, director of the NIH National Institute on Aging, which funded the analysis. "The national costs further compel us to do all we can to find effective treatments for Alzheimer disease and related dementias as soon as possible."

A press release from NIH noted that estimating the costs of dementia has been challenging. People with Alzheimer disease and other dementias often have multiple comorbidities. Moreover, estimating the value of family-provided or other informal care is difficult.

National Institute on Aging

"Resetting" the Addicted Brain

Researchers from the Intramural Research Program of the National Institute on Drug Abuse (NIDA; Bethesda, MD) and the University of California, San Francisco, reported in the April 18 issue of *Nature* (2013; 496:359–362) on a study in rats with results suggesting that targeted stimulation of the brain's prefrontal cortex could be a promising future treatment for addiction. The authors assessed nerve cell firing patterns in a rat model of compulsive drug seeking and showed that prolonged cocaine self-administration decreases the ex vivo intrinsic excitability of deep-layer pyramidal neurons in the prelimbic cortex, an effect significantly more pronounced in compulsive drug-seeking animals. Compensating for hypoactive prelimbic cortex neurons with in vivo optogenetic prelimbic cortex stimulation significantly impeded compulsive cocaine seeking, whereas optogenetic prelimbic cortex inhibition significantly increased compulsive cocaine seeking.

"This exciting study offers a new direction of research for the treatment of cocaine and possibly other addictions," said NIDA Director Nora D. Volkow, MD. "We already knew, mainly from human brain imaging studies, that deficits in the prefrontal cortex are involved in drug addiction. Now that we have learned how fundamental these deficits are, we feel more confident than ever about the therapeutic promise of targeting that part of the brain."

"What I find to be an exceptional breakthrough is that our results can be immediately translated to clinical research settings with humans, and we are planning clinical trials to stimulate this brain region using noninvasive methods," said Antonello Bonci, MD, NIDA scientific director and senior author of the study. "By targeting a specific portion of the prefrontal cortex, our hope is to reduce compulsive cocaine-seeking and craving in patients."

National Institute on Drug Abuse

Personal Choice in Predicting AD

Results of a survey presented at the 21st European Congress of Psychiatry in early April in Nice, France, suggested that some individuals would rather not know their own likelihood of developing Alzheimer disease (AD) in the future. Soboẃ, from the Medical University of Lodz (Poland) and colleagues reported on the results of a questionnaire administered to 68 cognitively intact elderly patients (age range, 62–75 y), 49 related caregivers of AD patients (age range, 42–74 y), and 96 4th-year medical students. Knowledge of AD was assessed, as well as willingness to undergo genetic or other testing that might predict later AD onset.

"Interestingly, in all the analyzed groups, subjects who are willing to have tests...score considerably lower on [knowledge about AD], so the less they know about Alzheimer's, the more enthusiastic about testing they are," Soboẃ said in his presentation. Medical students, predictably the group with most knowledge about AD, expressed the least willingness to undergo diagnostic tests (32%), compared with 40% of healthy elderly and 44% of caregivers. Medical students (40%) were also less likely to want testing even when close relatives had established AD diagnoses, with respective percentages of 55% and 61% in healthy elderly and AD caregivers. Almost all participants would be willing to undergo neuroimaging once they experienced symptoms of cognitive impairment.

The results were reported by Daniel Keller, MD, on Medscape on April 15 and will be published in the coming year.

Medscape