
**NewYork-Presbyterian Neurology and Neurosurgery**

2018 Report on Clinical and Scientific Innovations

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**Innovations at a Glance**

- One of 28 sites in a phase 2 clinical trial showing that the investigational anti-inflammatory drug ibudilast was superior to placebo in slowing the progression of brain atrophy in multiple sclerosis
- Conducted the first-ever dose escalation study using convection-enhanced delivery for diffuse intrinsic pontine glioma to bypass the blood-brain barrier and administer a drug directly to a brain stem tumor site
- Epigenome-wide study uncovers large-scale changes throughout the epigenome of the human Alzheimer's disease brain, revealing that tau-induced alterations of chromatin structure are much more profound than the changes that are attributable to amyloid pathology
- Investigated venous sinus stenting in patients with idiopathic intracranial hypertension, showing for the first time a quantitative reduction in intracranial pressure
- One of 25 clinical sites across the country for NeuroNEXT, an NIH-Network for Excellence in Neuroscience Clinical Trials created to expand capabilities for studies of promising new therapies for neurological diseases
- Created ALS Families Project to study relatives of individuals with amyotrophic lateral sclerosis who carry the same mutation to understand the earliest steps in its onset and how and why it develops
- Treated the first patient in a multicenter pivotal trial using focused ultrasound to address the major motor symptoms of Parkinson’s disease
- Identified the cell types and locations of origin of subependymomas, helping to improve diagnosis and treatment of patients with this rare disease
- Pioneered a minimally invasive posterior lumbar interbody fusion technique with cortical bone trajectory screws that are biomechanically stronger than pedicle screws, requires a smaller incision, and results in less muscle damage

NewYork-Presbyterian Neurology and Neurosurgery ranks #5 in the nation.
New Evidence of Cognition in Patients with Severe Brain Injury

Researchers at Weill Cornell Medicine have shown that measuring brain activity in response to hearing a brief narrative can identify patients with severe brain injury who have preserved high-level cognition despite showing limited or no consciousness at the bedside.

Their study, published November 21, 2018, in *Current Biology*, is the first to describe a method for measuring the delay in brain processing of continuous natural speech in patients with severe brain injury reflected in the electroencephalogram. The results correlated with evidence obtained using the now-established neuroimaging technique functional magnetic resonance imaging (fMRI) to identify the capacity to perform highly cognitively demanding tasks. Variations in degree of the delay in processing correlated with a range of remaining cognitive ability measured by behavioral assessments.

For this study, the Weill Cornell Medicine researchers, including first author Chananel Braiman, PhD, capitalized on the fact that the human brain produces electrical activity while following the variations in sound wave intensity in speech, called the natural speech envelope. They assessed the time delay in electrical brain activity with EEG in 21 patients with severe brain injury, including patients in vegetative, minimally conscious, and emerging from minimally conscious states, as they heard personally meaningful narratives recorded by family members. Previous studies have shown that personal stories in the voices of loved ones increase the probability of eliciting robust and reliable responses in brain-injured patients. The investigators also conducted EEG tests in 13 healthy people who heard a portion of the novel *Alice's Adventures in Wonderland*.

Next, the researchers conducted fMRI tests on the 21 patients with brain injuries while asking them to follow commands that prompted them to imagine they were playing tennis. Ten patients showed statistically significant brain activity during the command-following task compared to their resting states. After further analyzing this subset of 10 patients, the investigators found that these patients showed no statistically significant differences in their lag times for following natural speech measured in the EEG when compared to healthy participants.

The EEG response to the natural speech envelope also allowed the researchers to separate patients’ differing levels of behaviorally demonstrated cognition established by bedside behavioral evaluations using the JFK Coma Recovery Scale-Revised, which examines a patient’s arousal, communication, auditory, visual, verbal, and motor functions. “Once we placed patients who could carry out fMRI command-following tasks into a separate category, we were surprised we could clearly order patients into different diagnostic categories by average time delays observed in the EEG natural speech test,” says Dr. Schiff.

“This approach may be a more effective and efficient method for initially identifying patients with severe brain injuries who are very aware but are otherwise unable to respond, a condition called cognitive motor dissociation,” says senior author Nicholas D. Schiff, MD, the Jerold B. Katz Professor of Neurology and Neuroscience in the Feil Family Brain and Mind Research Institute and Co-Director of the Consortium for the Advanced Study of Brain Injury at Weill Cornell Medicine.

Several studies have previously shown evidence of highly preserved brain activity and overall patterns of sleep and wake electrical activity in people with brain injuries who can carry out fMRI mental imagery tasks. Researchers, including Dr. Schiff, have for example, previously found brain activity in some of such patients in response to commands to imagine they were playing a sport while undergoing fMRI testing. However, fMRI is not an efficient or universally effective screening tool for these patients: It is expensive, and it cannot be used for those with pacemakers or implanted metal hardware as a result of their injuries. By contrast, EEG passively measures electrical brain signals through small electrodes placed on the scalp, can be used for longer periods, and is a less expensive testing method.

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Reference Article
Validating an MRI Measure of Pathology in Alzheimer’s Disease

Researchers in the Department of Neurology and the Taub Institute for Research on Alzheimer’s Disease and the Aging Brain at Columbia University Irving Medical Center have developed a quantitative MRI measure that reflects the joint contributions of neurodegeneration, brain infarcts, and white matter hyperintensities (WMH) to the clinical and pathologic diagnosis of late onset Alzheimer’s disease (LOAD). WMH is presumed to be an indication of small vessel cerebrovascular pathology.

“The goal of the study was to develop a quantitative metric combining cerebrovascular and neurodegenerative factors into a single conceptual framework that closely reflects the mixed pathology of late-onset Alzheimer’s disease,” says Richard Mayeux, MD, MSc, Neurologist-in-Chief, NewYork-Presbyterian/Columbia University Irving Medical Center.

“The quantitative MRI measure was derived from the Washington Heights-Inwood Columbia Aging Project cohort by linearly combining individual cerebrovascular and neurodegenerative factors weighted by their association with episodic memory,” according to Adam Brickman, PhD, Associate Professor of Neurological Sciences in the Taub Institute.

The Washington Heights-Inwood Columbia Aging Project, which is a prospective, community-based longitudinal study of aging and dementia in northern Manhattan, provided individuals recruited from Medicare recipients in three waves – 1992, 1999, and 2009 – who were followed every 18 to 24 months. Structural MRI scans were acquired in 1,333 participants of which 1,175 met the following criteria for participation:

- available quantitative MRI data
- complete neuropsychological evaluations performed at the baseline and follow-up visit concurrent with the MRI scan
- no evidence of dementia at the clinical follow-up visit prior to the scan

The researchers forward applied the score to independent samples and performed further validation by demonstrating its association with neuropathology at autopsy, clinically proven LOAD biomarkers, and conversion from mild cognitive impairment to LOAD.

The investigators noted that “because the MRI measure comprised neurodegenerative changes such as cortical thinning and hippocampal atrophy – well-validated MRI biomarkers for LOAD – it is not surprising that it correlated with memory and measures of pathologic findings in LOAD.” The study further indicated that the “MRI measure was also associated with both LOAD neuropathology and related PET and cerebrospinal fluid biological markers, an important validation step.”

The results of the study, which were published in the October 9, 2018, issue of Neurology, with an accompanying editorial, confirm and augment the role of both neurodegeneration and cerebrovascular pathology in LOAD and suggest the possibility of capturing both in a single valid and reliable MRI-based measure that can be used for clinical purposes and potentially for research.

Reference Article

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Advancing Alzheimer’s Disease Research through Multi-omics Data

Since Alzheimer’s disease was first described in the early 1900s, clinicians and scientists the world over have dedicated their careers to studying the pathobiology of this most common form of dementia in the hopes of developing methods of prevention, treatments to halt progression, and ultimately a cure. While the gains in understanding have been limited, today’s high-throughput technologies are revolutionizing neurological research. From the genome to the microbiome and several omics in between, data are being generated that can provide significant biological insights into the disease.

In the Center for Translational & Computational Neuro-Immunology at Columbia University Irving Medical Center, Philip L. De Jager, MD, PhD, the Center’s Director, and colleagues in the Rush Alzheimer’s Disease Center of Rush University in Chicago, have taken advantage of these technologies to create a multi-omics atlas of the human frontal cortex to help drive data-driven progress in aging and Alzheimer’s disease research.

The researchers undertook a systematic profiling of the dorsolateral prefrontal cortex obtained from a subset of autopsied individuals enrolled in the Religious Orders Study (ROS) or the Rush Memory and Aging Project (MAP), which are jointly designed prospective studies of aging and dementia.
Advancing Alzheimer’s Disease Research through Multi-omics Data  (continued from page 3)

With over 3,300 subjects, the databases of these projects house detailed, longitudinal cognitive typing during life and a quantitative, structured neuropathologic examination after death. Due to its prospective design and recruitment of older, non-demented individuals, the data can be repurposed to investigate a large number of syndromic and quantitative neuroscience phenotypes. The many subjects that are cognitively non-impaired at death also offer insights into the biology of the human brain in older non-impaired individuals. A number of additional layers of data, including proteomic and metabolomic data, from tissue samples and purified cell populations are being produced and will become available as the data are finalized. The first generation of data now available are outlined in the table.

All of the data are publicly available to investigators and have been used to power the discovery of new Alzheimer genes and the development of new approaches to develop therapies for Alzheimer’s disease by investigators at Columbia University and throughout the world.

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</table>

*Chromatin immunoprecipitation with sequencing using an anti-Histone 3 lysine 9 acetylation (H3K9Ac) antibody
**The data identified are available to prospective researchers at synapse.org.

Reference Article

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