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# Technological Advances Provide New Ways to Study the Brain

*Scientists develop innovative tools to improve methods for viewing, mapping, and analyzing the brain*

**CHICAGO —** With the launch of the BRAIN Initiative and similar projects around the globe, new tools and techniques are being developed that will change the way neuroscientists study the brain. Advances in computer software allow scientists to quickly create three-dimensional models of brain regions and compile larger models that span the entire brain. Innovations in stem cell technology are providing researchers with a new way to study human diseases, while other technological advances have led to the development portable and wireless devices that offer ways to image brains in moving subjects for the first time.

The projects were described at Neuroscience 2015, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Today's new findings show that:

- Scientists are developing a portable brain scanner that will allow subjects to move around while it takes high-resolution images of structures deep within the brain (Julie Brefczynski-Lewis, abstract 558.04, see attached summary).
- New software provides scientists with a way to quickly and easily create three-dimensional models from large datasets (Cameron Christensen, abstract 598.19, see attached summary).
- A new process for constructing models of the brain, without bias toward a certain brain region, lets researchers simulate brain-wide activity in the mouse (Marc-Oliver Gewaltig, abstract 515.05, see attached summary).
- Stem cell technology enables scientists to thoroughly characterize the molecular differences between healthy and diseased cells, which could lead to better-targeted treatments for neurological diseases (Clive Niels Svendsen, abstract 219.24, see attached summary.)
- Recordings from the brains of bats during flight reveal how they use echoes to map three-dimensional space and how sensory and motor information is integrated in the brain (Ninad Kothari, abstract 90.15, see attached summary).

"Recent innovations in technology, such as those described today, are revolutionizing neuroscience," said Terry Sejnowski, PhD, of the Salk Institute for Biological Sciences, moderator of the session and an expert in computational neuroscience. "Advanced models of the brain will allow us to better understand the brain in both health and disease, which will lead to more successful treatments in the future."

This research was supported by national funding agencies such as the National Institutes of Health, as well as other private and philanthropic organizations. Find out more about tools and technology in neuroscience research at *BrainFacts.org.*

**Related Neuroscience 2015 Presentations:**

Special Lecture: Nanoscopy with Focused Light: Principles and Applications
Sunday, Oct. 18, 1-2:10 p.m., Hall B1

Symposium: Early Reports from the BRAIN Initiative Frontline: Advancing Technologies to Accelerate Our Understanding of Brain Function
Monday, Oct. 19, 8:30-11 a.m., S100A

# Abstract 558.04 Summary

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## Scientists Are Developing a New High-Resolution Portable Brain-Scan 'Helmet'

*Technology has potential to dramatically expand our knowledge about the brain and its disorders*

Researchers have designed a wearable brain-scanning device that can be used while a person is upright and moving rather than lying down. Simulation studies of the new technology, called Ambulatory Microdose Positive Emission Tomography (AMPET), indicate that it is more sensitive and requires a smaller dose of radioactive material than conventional imaging. The technology was presented at Neuroscience 2015, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Current imaging technology forces a choice between portability and high image resolution. Large, "bolted-to-the-floor" equipment, such as those used for magnetic resonance imaging (MRI), magnetoencephalography (MEG), and traditional PET, provides high-resolution images but requires the participant to remain completely still. Others, such as electroencephalography (EEG) and near-infrared spectroscopy (NIRS), work with a moving subject, but they have very low spatial resolution and do not reveal structures deep within the brain, such as the hippocampus (used in memory and navigation) and the amygdala (important for emotion).

By contrast, the AMPET "helmet" can be worn while the subject is upright and moving, and, according to early research, has the potential to produce high-resolution images of the whole brain, including deep structures. Simulation studies have shown AMPET is more sensitive and will require a smaller dose of radioactive material than is currently used with conventional imaging.

Although only in its prototype stage, AMPET has a wide variety of potential research and clinical applications. This brain-scan "helmet" could, for example, help scientists better understand how exercise affects brain-injury recovery, the role of myelin in multiple sclerosis, and how specific brain chemicals influence disease and behavior.

"Imagine imaging a savant while painting or a chess master in action: We might be able to tap into the mechanisms behind these super abilities," said lead author Julie Brefczynski-Lewis, PhD, of West Virginia University. "Clinically, we may better understand why people with autism react differently to social situations and this may inform diagnosis and therapies. Moving forward, we'll be talking with researchers and clinicians working in stroke rehabilitation, Parkinson's disease, and balance disorders, as well as neuroscientists who study social, cognitive, and emotional processes, to determine how such a scanner could be used and what features are most necessary."

Research was supported with funds from the BRAIN Initiative Next Generation Human Imaging Award and the National Institute of Mental Health.

Scientific Presentation: Tuesday, Oct. 20, 1-3:30 p.m., S102

558.04, Ampet: a brain initiative planning project to design a wearable, microdose pet imager
***J. A. BREFCZYNSKI-LEWIS**[1], S. MAJEWSKI[2], R. MANJESHWAR[3], A. STOLIN[1], P. KINAHAN[4], J. QI[5], S. DOLINSKY[3], R. HARRISON[4], M. RISHEL[3], B. ELSTON[4], K. GONG[5], K. VAIGNEUR[6];
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TECHNICAL ABSTRACT: Brain imaging has been limited by the motion intolerance of big, bolted-to-the-floor imagers like MRI, PET and MEG and by low resolution, surface-only imaging of EEG and Near Infrared Imaging. In this project, we are designing a wearable imager that will enable high resolution imaging of both deep and surface brain, all while the subject is upright and moving. Our initial simulation results have shown a more than 400% increase in sensitivity by the helmet scanner over the conventional whole-body PET scanner. With further improvements in time-of-flight (TOF) and depth of interaction information, we expect the injected radioligand dose can be very low. Pilot data results show that it will be better than 1/10th of the standard dose. Advances will be shown, including designs of physical detectors and mechanical support prototypes, including one that is worn like a backpack and allows a high degree of motion freedom. Our team has investigated potential uses in the neuroscience and clinical worlds. Application ideas will be discussed, including those enabled by different uses of radioligands such as low-dose O15 with its relative short half-life that will allow for functional PET imaging, and other studies utilizing different neurotransmitter and microglia targets. Novel areas of study may include balance, physical therapies, natural social interactions, virtual reality as well as disorders like stroke, Alzheimer's, Parkinson's, multiple sclerosis and traumatic brain injury (e.g. testing effects of exercise on brain recovery). By helping future users of the imager understand the different design optimizations necessary to account for sensitivity, resolution, brain coverage and weight of detector (freedom of movement), we can discover the best uses for our imager and focus on creating the best prototype designs, while developing future partnerships.

**Abstract 598.19 Summary**

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## Researchers Create Faster Method of Generating 3-D Models From Brain-Imaging Data

*Advance will help translate large datasets for a deeper understanding of the brain*

Researchers have successfully adopted existing computer software into a new platform that provides a simpler and faster way of creating three-dimensional models from the massive quantities of data produced by neuroimaging techniques. This new method has the potential to greatly reduce the time that researchers and clinicians must wait between taking images of the brain and gaining scientific and medical insights from the data. The research was presented at Neuroscience 2015, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

In order to understand brain function, neuroscientists must understand the connections between neurons and how groups of neurons work together in circuits. Recent advances in imaging have made it easier than ever to see these connections, but the number of neurons in the brain makes for an enormous amount of data. For example, a high-resolution scan of an area of the brain the size of a penny would generate approximately 2 million images, requiring about 12 terabytes of computer memory storage.

To help overcome that challenge, researchers created a new method for using the software technology known as ViSUS (Visualization Streams for Ultimate Scalability), which allows them to process imaging data using less memory and with increased speed. The researchers tested the procedure on the visual cortex of primates. After labeling a set of neurons, they used a technique called CLARITY to make the surrounding brain tissue transparent. They then streamed the images taken via ViSUS, which allowed the researchers to see the images as they were acquired, rather than waiting for the dataset to be fully downloaded. To save time, low-resolution images were streamed first. If there was a particular area of interest, the researchers could zoom in on it with high resolution. The program can be run on a typical computer or laptop.

"We are currently working to create a simple point-and-click interface to make the importing, alignment, and manipulation of images accessible to all researchers, regardless of their knowledge of computers," said lead author Cameron Christensen of the University of Utah.

Research was supported with funds from the National Institutes of Health, the National Science Foundation, and Research to Prevent Blindness.

Scientific Presentation: Tuesday Oct. 20, 3-4 p.m., Hall A

598.19, Large scale imaging and 3D visualization of long-range circuits in clarity-treated primate visual cortex
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TECHNICAL ABSTRACT: Understanding the circuitry of the brain is necessary to understanding brain function. Recently there has been a renaissance in neuroanatomy, thanks to the discovery of cell-type specific tracers, and new methods for high-resolution imaging and 3D reconstruction of large data sets at much greater speed than previously possible. However, the large size and complexity of the primate brain, compared to mouse brain, poses greater challenges to the study of neural circuits. CLARITY tissue clearing (Chung et al. 2013) allows imaging labeled circuits through entire tissue blocks, without the need for tissue sectioning and section-to-section alignment. However, the large primate brain requires long image acquisition times, and software capable of compiling and stitching very large data sets, and tracing through these volumes.

Here we have labeled projection neurons between visual cortical areas V1 and V2 in primates, using GFP-expressing AAV9. Tissue blocks were cleared using passive CLARITY technique (PACT; Yang et al. 2014), and imaged in a 2-photon microscope. A 1mm diameter injection site in V2 labeled a field of axons in V1 of about $60mm^3$. Imaging a $5mm^3$ volume at 1 µm z-resolution took 96 hrs, generating 130 GB of data. Hence, imaging the $60mm^3$ V1 block would take 19 days, and produce 1.6 TB of data.

To address the challenges posed by handling large data sets we adopted the ViSUS streaming platform for scalable data analysis and visualization (Pascucci et al. 2012). This is designed around an innovative notion of hierarchical space-filling curves that enables selective data access both locally and remotely. Its combination with progressive algorithms enables a dynamic scripting layer that provides on-the-fly computation of derived quantities such as statistics on the data or multiple concurrent maximum intensity projections from arbitrary directions. Remote data access is enabled with a server. View-dependent, progressive resolution data streaming allows clients fast access to regions of interest while client-side caching amortizes network transfer costs, effectively hiding them from the user. Eventually we will locate the server directly at the acquisition source to allow immediate data conversion so that the 3D images can even be viewed during acquisition.

The ease of data access provided by the ViSUS framework facilitates the alignment of 3D volumes while providing interactive access to the full data collection, so that a user can more easily switch among the tasks of data alignment, analysis and annotation. The end result is the presentation of data collections as single, large volumes that can be handled easily and interactively by multiple users in collaboration over a distributed environment.

## Abstract 515.05 Summary

Senior Author: Marc-Oliver Gewaltig, PhD
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### New Tool Can Create Complex Models of the Mouse Brain

*Semiautomatic tool designed to integrate data without bias toward particular brain region*

A new tool can create complex models of the whole mouse brain, providing a more comprehensive look at the brain than was previously possible. Researchers unveiled the tool today at Neuroscience 2015, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. Models of the brain such as these can help researchers understand how the brain works by allowing them to simulate responses to certain inputs or test what happens when particular circuits are activated.

In order to understand the brain at the level of individual neurons and synapses, scientists often build computer models of neuronal circuits or particular brain regions. However, while some regions, such as the visual cortex, have been the focus of many such studies, other areas of the brain are largely ignored, and a comprehensive model that can simulate activity across the entire brain does not yet exist. In order to create whole-brain models, the researchers developed a semiautomatic workflow that can piece together imaging data from all brain regions and be run on state-of-the-art simulation systems.

The researchers used images from the Allen Mouse Brain Reference Atlas, first identifying the position and type of each cell, then adding connections between the cells and brain regions by integrating information from the Allen Mouse Connectivity Atlas and the Swiss Blue Brain Project. The resulting model — which covered the entire brain — was fed into simulators that the group had created in earlier work. The simulators connected the brain model to a virtual mouse body; if the whiskers of the virtual mouse were touched, the same brain areas that would be activated in a live animal also lit up in the model. Because of the way the workflow is designed — to integrate data without bias toward a certain brain region — it will be able to be used for any species of animal, not just mice.

Senior author Marc-Oliver Gewaltig, PhD, of EPFL's Center for Brain Stimulation in Geneva, Switzerland, sees the model as a guide for new research, one that can be continually and systematically improved upon. "Although the resulting models are far from perfect, they still represent the whole brain without a bias towards a particular region or area," he said. "They give us the capability to build complex brain models on a routine basis."

Research was supported with funds from the Blue Brain Project and the European Human Brain Project.

Scientific Presentation: Tuesday, Oct. 20, 8-9 a.m. Hall A

515.05, Data-driven construction of mouse whole-brain models
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TECHNICAL ABSTRACT: We present a semi-automatic process for constructing whole-brain models at the point neuron level from different sets of image stacks. Our process has two parts, each with several steps. In the first step, we determine the positions of all cells, using high-resolution Nissl stained microscope image stacks Allen Mouse Brain Reference Atlas [1]. In the second step, we determine the type of each cell, using In situ hybridization (ISH) image data from the Allen Mouse Brain Atlas. To increase the spatial resolution of the data, we re-aligned the ISH images to the reference atlas. Here we present differentiation into glia, excitatory neurons and inhibitory neurons. More fine-frained differentiation is possible by adding more genes to this step. We compare the resulting cell and neuron numbers to literature data [2,3]. Our estimates of cell numbers are best for the isocortex (relative error 5%) and worst for the cerebellum (60%), where the cell density in the images is too high to distinguish individual cells. After differentiating glia and neurons, our estimates differ from the literature value by an average of 12% for the isocortex and 63% for the cerebellum. In the next step, we use two-photon tomography images of rAAV labeled axonal projections from the Allen Mouse Connectivity Atlas to determine the mesoscale connectivity between the neurons in different brain regions. For this step, a comprehensive comparison to experimental data is difficult, due to lack of comparable connectivity data.
Finally, we obtain a network model that can be simulated with state-of the art simulators like NEST and NEURON. We show results from a simulated whisker stimulation experiment and compare the evoked activity patterns to data from comparable calcium imaging experiments. We also present results from our ongoing research on reconstructing the microscale connectivity between the neurons in a small volume from appropriate data-sets.
[1] Allen Mouse Brain Atlas (Reference Atlas Version 2 (2011)) , Allen Mouse Connectivity Atlas, http://www.brain-map.org
[2] Herculano-Houzel S et al. Front. in Neuroanatomy 2013; (DOI:10.3389/fnana.2013.00035)
[3] Herculano-Houzel S et al. Brain Behav Evol 2011;78:302-314 (DOI:10.1159/000330825)

**Abstract 219.24 Summary**

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## Advances in Stem Cell Technology Will Help Identify Molecular Characteristics of Diseases

*Scientists hope the new process of characterizing cells will reveal novel drug targets*

New technology allows researchers to characterize the differences between healthy and diseased neurons like never before, according to a study released today at Neuroscience 2015, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. Using human cells from patients with neurological disorders and healthy controls, the new strategy will help identify what goes wrong in different diseases. The technology described will also make the identification process cheaper, faster, and more reliable.

Different cell types in the brain vary in subtle ways, and understanding these differences might explain why some cells become diseased and how to make drugs that can correct the problem. However, for ethical reasons, studying human brain cells has been difficult, until the recent development of induced pluripotent stem cell (iPSC) technology. iPSCs are adult cells — often skin cells — that can be reprogrammed to become different types of cells — such as neurons — through a process that involves turning certain genes on or off.

In this work, the researchers wanted to define different characteristics of healthy and diseased cells. Using iPSC technology, they created 16 different cells lines, some using cells from healthy humans and others using cells from people with amyotrophic lateral sclerosis (ALS) or spinal muscular atrophy and containing the specific mutations associated with those diseases. The researchers programmed the cells into motor neurons, the type of neuron most affected by ALS and spinal muscular atrophy. Next, they did a thorough characterization of each cell line, looking at the sequence of the genome, what RNA is made, how the DNA is modified to control the expression of certain genes, and which proteins are present. They also completed extensive imaging. By detailing the cells so thoroughly, the researchers hope to identify patterns and specific characteristics of diseased and healthy cells.

"Ultimately, we envision these analyses leading to the identification of a network of unique signatures relevant to motor neuron disease," said lead author Clive Niels Svendsen, PhD, from the Cedars-Sinai Medical Center. "These insights will provide molecular targets that can be used to develop new drugs to block the progression of these motor neuron diseases, which are presently untreatable."

Research was supported with funds from the National Institutes of Health.

Scientific Presentation: Sunday, Oct. 18, 4-5 p.m., Hall A

219.24, Establishing the molecular signatures of motor neuron cultures derived from ALS, SMA and control induced pluripotent stem cells
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TECHNICAL ABSTRACT: Subtle variations amongst different cell types in the central nervous system (CNS) remain undefined, which has complicated the successful discovery of disease-modifying therapies for neurodegenerative diseases. There is a critical need to define the state and predict the behavior of healthy and diseased human cells in the CNS. Our knowledge of the CNS and the ability to intervene rationally in disease would be dramatically advanced by generating quantitative molecular phenotypes_essentially cell signatures_of human neurons, astrocytes and oligodendrocytes from healthy people and from patients with CNS disorders such as the motor neuron diseases. Despite this desperate need, the inaccessibility of human brain cells has made studying them difficult until the hallmark discovery of cellular reprogramming and the induced pluripotent stem cell (iPSC) technology. The NeuroLINCS consortium has generated 16 total iPSC lines from amyotrophic lateral sclerosis (ALS) patients with the C9orf72 (4) or SOD1 mutations (4), spinal muscular atrophy patients (4) and control subjects (4). Motor neurons, the primary cell type affected in these diseases, were generated from the iPSCs under specific differentiation protocols. Transcriptomics, epigenomics, whole genome sequencing, proteomics, high content imaging, high throughput longitudinal single cell analysis and other cell-based assays are all in progress using standardized and parallel cultures. Specific "omics" profiles are associated with these different motor neuron diseases (or "genetic perterbagens"). Integrated signatures are currently being generated using bioinformatics, statistics and computational biology to establish patterns that may lead to a better understanding of the underlying mechanisms of disease. We are also developing innovative software tools and approaches that will make the comprehensive signature generating process faster, and more reliable. All of this data will be made available through the NIH LINCS program for the entire scientific community to utilize.

**Abstract 90.15 Summary**

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## Neural Recordings From Flying Bats Aim to Show How Bats Navigate

*Scientists combine recordings with new 'echo model' to reveal how 3-D space is represented in the brain*

Using wireless technology and computer modeling, researchers have simulated how bats use ultrasonic vocalizations and echo reflections to navigate. The results enable better understanding of how sensory information is represented in mammals' brains and how that information allows them to interact with objects in three-dimensional space. The findings were presented today at Neuroscience 2015, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

As bats fly, they produce ultrasonic sounds that reflect back from objects in the environment. Bats listen to these echoes and use them to navigate — to plan where they are going and to track and capture prey. In order to understand how bats use echoes to construct three-dimensional space in their minds, researchers recorded from the brains of flying bats.

Bats were trained to fly through a room, avoid obstacles, and land on a platform to receive a food reward. As they flew, the bats' vocalizations and flight trajectories were recorded. The researchers then combined the sounds the bats made and their flight patterns to create an "echo model" that reconstructed the echoes heard by the bats during their flight. Neural activity in the superior colliculus — an area important for orienting oneself in space — was also recorded during flight via a wireless device the bats carried. The researchers recorded from both sensory neurons of the intermediate layers and motor neurons of the deeper layers of the superior colliculus, with the goal of revealing how integration between sensory signals and motor systems might occur. Using the echo model and the neural recordings, the researchers were able to construct how neurons in the superior colliculus represent 3-D space.

"Our results are the first to report neural activity from a sensorimotor area — the superior colliculus — in a flying animal," said lead author Ninad Kothari, PhD, from Johns Hopkins University. "Our findings help us better understand how three-dimensional space is represented in the mammalian brain and how, using this information, an animal makes movements to interact with objects in 3-D space."

"Understanding how sensory and motor information is integrated in the brain should be extendable to other mammals, including humans," Kothari added.

Research was supported with funds from the National Science Foundation, the Air Force Office of Scientific Research, and Human Frontiers.

Scientific Presentation: Saturday, Oct. 17, 3-4 p.m., Hall A

90.15, Neural activity in the SC of a flying echolocating bat
***N. B. KOTHARI**[1], M. J. WOHLGEMUTH[1], C. F. MOSS[1];
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TECHNICAL ABSTRACT: The superior colliculus (SC) is a laminated midbrain structure implicated in species-specific orienting behaviors. Previous recordings from the SC of head restrained and passively listening bats revealed two classes of cells: 1) neurons that encode 2D head-centric space (azimuth and elevation) around the bat and 2) 3D neurons that encode not only the azimuth and elevation but also range. Range is encoded by neurons that exhibit pulse-echo delay tuning. SC recordings from bats resting on a platform and tracking a moving target revealed vocal-premotor activity prior to each sonar vocalization. Here we present extracellular recording data from the SC of freely flying bats, and characterize sensory, sensori-motor and motor neural activity. We trained big brown bats to locate and land on a platform for a food reward. While the bat performed this task, single unit activity was recorded across the SC laminae using a telemetry system. Synchronized with neural recordings, high-speed audio and video recordings captured the bat's echolocation, head aim and flight behaviors. To reconstruct the timing of the echoes arriving at the bat's ears, we developed an echo model using the recorded sonar vocalizations, the bat's 3D head aim and position in space. Correlating echo timing information with neural activity we characterize neurons that respond to echoes from different objects along the bats flight trajectory. Correlating the neural activity with the sonar vocalizations we find sensory-motor and motor neurons in the intermediate and deeper layers of the bat SC. Recording simultaneous activity across the SC laminae allows us to observe the integration of information across these functional layers. Such integration of information is essential for spatial navigation, orientation and prey capture by echolocating bats.