

Thomas Grabowski, Director of the UW Alzheimer's Research Center, works to improve the potential of functional brain imaging to diagnose early Alzheimer disease. Photo credit: Elizabeth Myers

Research at the UW Will Improve How Clinicians Help Those with Memory Loss

By Genevieve Wanucha, SM

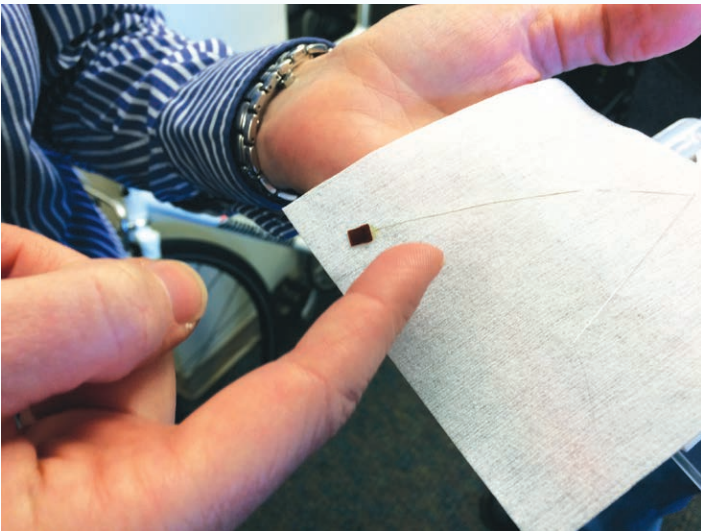
Giuseppe sits in a small room, joystick in hand, playing a video game. He zooms through a grassy field, foraging for big yellow bananas. Banking left, he speeds along a stone wall and captures two. A sweet treat rolls down a tube into his mouth, and he munches on his reward. Giuseppe, a monkey, is a research participant in the Buffalo Lab at the University of Washington.

In the lab next door, researchers watch a thin yellow line zigzag across a computer screen with a loud crackling sound. "That's the sound of a neuron firing an action potential," says graduate student Seth Koenig, who is recording the activity of single neurons in the monkey's brain via a hair-thin electrode implanted into the medial temporal lobe. A camera setup tracks Giuseppe's eye movements.

Along with four other monkeys trained to play various computer games, Giuseppe is helping researchers figure out how the primate brain forms memories—and offering clues to interventions for the memory impairments of Alzheimer's disease in humans at the same time.

Gaming the memory system

Humans and monkeys have very similar brain anatomies, making the primate brain a valuable model for human neurobiology. We also share the ability to perform very complex tasks. In fact, this macaque monkey can play a more difficult version of this game. He enters the same green field and discovers it's been cleared of bananas. There's a reward only if he can navigate back to the spot where a banana was on his previous pass; when he returns to the same spot, the banana will reappear.



The Buffalo Lab inserts hair-thin electrodes deep into the monkey brain to monitor neurons during memory formation. *Photo credit: Beth Buffalo*



Beth Buffalo plays the video game designed for her lab's monkeys. *Photo credit: Beth Buffalo*

"To successfully remember the banana's location, he must pay close attention to where he is in his environment," says Beth Buffalo, Associate Professor in the UW's Department of Physiology and Biophysics, who designed these video games and has worked with monkeys since high school. "He needs to get a sense of where the banana is relative to his position and use the landmarks to help guide him." By doing so, Giuseppe will successfully encode a memory, which he can use later to retrace his steps to the invisible fruit's location.

The monkey's ability to complete such a memory task may hinge on a particular type of neuron, a "grid cell," found in the medial temporal lobe. Grid cells may help our brains create representations of newly encountered environments, which are known as "cognitive maps." Buffalo thinks these maps help us remember the dimensions of a physical space, as well as aspects of time and sensation: how long it takes to get around, and sights and sounds we find there, for example. This comprehensive record of new experiences helps us plan future trips.

The medial temporal lobe in humans happens to be the first spot where the tangles of Alzheimer's disease pathology build up and eventually kill neurons. The disease rips apart a lifetime of cognitive maps, which explains why a person's first clinical symptoms often begin with having trouble finding his or her way home from the grocery store, or even around the house.

Alzheimer's disease, a neurodegenerative condition that impairs memory and cognitive ability and leads to dementia, affects 5.4 million Americans. This number includes 100,000 people younger than age 65. It is the only chronic disease currently without an effective treatment, and the number of cases is predicted to expand to 16 million by 2050 as baby boomers age, overburdening the national health care system and family finances.

"In order to understand what might be missing or impaired in human patients with Alzheimer's disease, we need to understand

how memory system works at a deep level," says Buffalo. "We hope to model the processes of healthy cognition, reflected in eye movements and brain function, which can then be differentiated from impaired cognition."

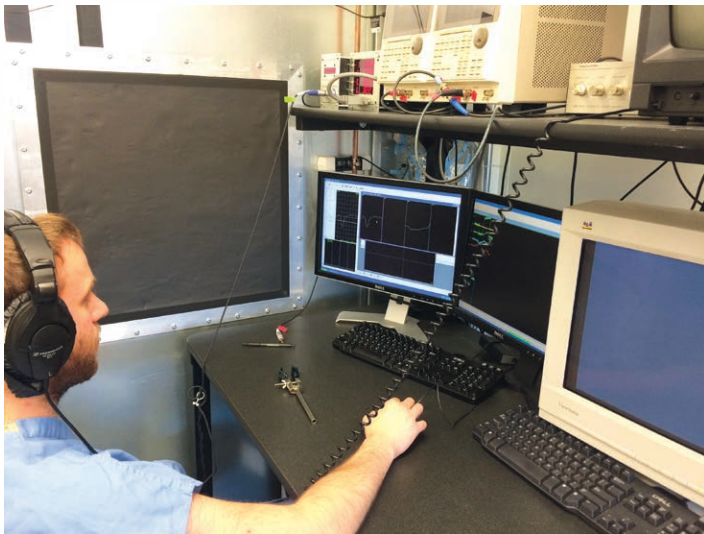
To this end, the Buffalo team has found several biological markers of memory formation in the brain—distinct patterns of neuron firing and eye movements that predict a monkey's success or failure in a memory task. Aligned with the focus of the UW Alzheimer's Disease Research Center (ADRC), Buffalo's goal is to translate these cognitive biomarkers into ways to identify signs of memory loss in people, even when there are no noticeable symptoms—a development that could lead to earlier diagnosis and a window for intervention. And she is close to reaching that goal.

All eyes on the prize

When she ran her lab at Emory University, Buffalo and her colleagues learned that the primate hippocampus in the medial temporal lobe plays a key role in guiding the eyes around a scene based on memories of a prior viewing. Because Alzheimer's disease in humans targets the hippocampus, Buffalo reasoned that signs of developing disease first appear in eye movements. Specifically, people with mild cognitive impairment would look around an image differently than normal controls, just like monkeys with damage to the hippocampi.

Buffalo and her colleagues designed a computer task meant to assess memory impairment. In a five-year NIH-sponsored study, published in 2013, this task predicted whether participants with mild cognitive impairment would worsen within four years. Surprisingly, poor performance on the first round of this test predicted cognitive decline, even in individuals in the healthy cohort.

"That result got us interested in the possibility that this noninvasive behavioral diagnostic tool detects hippocampal abnormalities associated with Alzheimer's disease and can predict cognitive



Graduate student Seth Koenig watches the electrical activity of a neuron in a monkey's hippocampus. Photo credit: Beth Buffalo

decline," says Buffalo. "And it only requires a laptop camera." Fast-forward to 2016, when Buffalo is cofounder of a company called Neurotrack, which has developed a five-minute computer-based visual test for memory impairment in humans called Imprint™.

If Neurotrack succeeds in bringing Imprint into doctor's offices, the test would serve as a quick, easy, and affordable way to detect the very earliest manifestations of dementia. A potentially revolutionary tool, Imprint could allow patients to receive a personalized risk assessment in the doctor's office, empowering him or her to pursue promising lifestyle strategies to maintain cognitive function or a new therapeutic.

Along with plans to make Imprint available for routine clinical use, Buffalo hopes to collaborate with ADRC. She thinks the app can serve as a tool to validate the results of ongoing brain imaging studies or clinical trials by helping researchers correlate measurements of memory with other biomarkers in spinal fluid, blood, or brain images.

In one of these studies, ADRC Director Dr. Tom Grabowski and Tara Madhyastha, a Research Assistant Professor in the Department of Radiology, are using functional magnetic resonance imaging (fMRI) to study the brain network connectivity in ADRC research participants. They want to establish what Madhyastha calls the holy grail of neurodegenerative research—whether fMRI scans can detect and track disease in individuals, and whether PET scan images of brain blood flow replicate and confirm fMRI results. If so, the field would be a step closer to using one brain scan to monitor the effectiveness of a drug in a clinical trial.

Messages in our genes

The UW's ADRC, one of the country's top NIH-sponsored centers for Alzheimer's research, recently shifted its focus to precision medicine. Endorsed as President Obama's "moon shot," this approach has revolutionized cancer and cystic fibrosis treatment

by tailoring treatment plans to each individual's unique profile of biomarkers, especially genetic risk factors.

"A precision medicine approach to Alzheimer's disease runs about a decade behind oncology," says Grabowski, "but we hope that the ADRC's 30-year legacy in neurogenetics will lead to more personalized, effective treatments for patients."

From its early days, the ADRC has led the discovery of genetic causes of Alzheimer's disease and frontotemporal degeneration (FTD). Now, Suman Jayadev, Assistant Professor of Neurology at UW, is harnessing this knowledge with advanced genetic technology. She leads a project to establish the role of exome sequencing in clinical decision-making.

The exome is the 2 percent of the 3.2 billion bases of the human genome that codes for proteins. This small-but-mighty slice of DNA is the part of the genome that researchers know enough about to infer the pathological consequences of variations in its code. So sequencing the exome, rather than the whole genome, is currently the most practical way to identify the genetic culprits in many diseases.

Whole exome sequencing is effective in cases of neurodegenerative disease, such as Alzheimer's and Parkinson's diseases, ALS, and frontotemporal degeneration (FTD), because they often have a genetic basis. About 30 percent of cases carry some genetic risk factor. As more and more affected families demand information about their risks, treatment options, and eligibility for clinical trials of targeted therapeutics, this technology is gaining a place in the precision medicine tool chest.

Jayadev, who studies gene mutations in the lab and counsels people at risk for Alzheimer's disease, is intimately familiar with the disconnect between what patients want to know and what she can tell them. "I'm very interested in how personal exome



The UW ADRC aims to speed the development of treatments tailored to a person's genetic risk factors. Image credit: Ernesto del Aguila III, NHGRI

sequencing will change the management of dementia patients, affect expectations of their physicians, and further the quest for treatments," she says.

With philanthropic support from the Ellison Foundation, Jayadev is running what is essentially a dress rehearsal of a precision medicine-era dementia clinic. The cast includes an exome sequencing team at the UW Center for Precision Diagnostics, a neurogeneticist, a genetic counselor, and a cohort of people who have early stage dementia or a family history of dementia but no known genetic mutation.

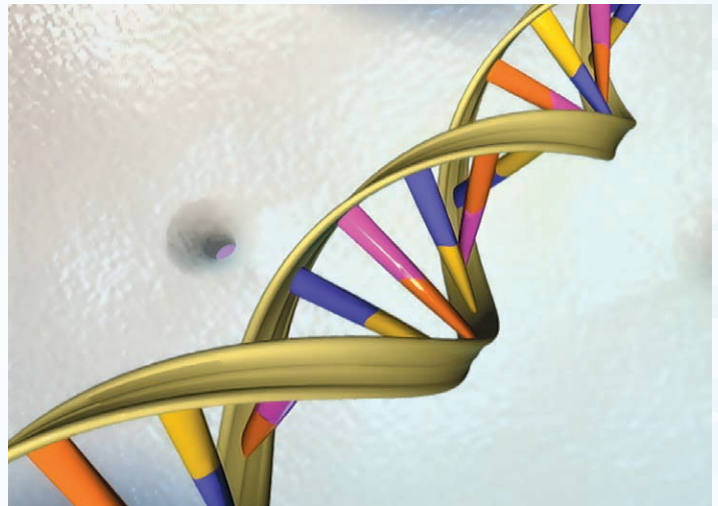
The study participants, who have agreed to learn the results of their exome sequencing, may finally get an answer to their question: "Why me?" Others will learn that they carry a rare genetic variant, but that it's not certain how much it raises their risk of developing dementia in the next decade. Brad Rolf, a genetic counselor at UW, will evaluate what works and what doesn't work in the conversations, whether people get what they expect, and how that translates to satisfaction.

From Rolf's perspective, there's far-reaching value in creating a model for exome-based genetic counseling in neurology. "Many neurologists have taken a special interest in genetics because so many of the conditions they see have a genetic basis," he says. "In the future, more providers who don't have an expertise in genetics will be ordering exome-sequencing tests. We hope that a summary of our experience can help provide guidance for genetic counseling in this particular population, especially as single-gene tests are phased out and exome sequencing becomes a first-line choice."

On the research side, Jayadev and her team have no small task. She aims to amass and characterize the different genetic fingerprints that mark neurodegenerative conditions in patients. The idea is to group people based on their underlying biochemical flaw. This risk stratification gives a glimpse at how precision medicine in Alzheimer's disease would actually work—guiding precise diagnoses and selection of presymptomatic participants for clinical trials of therapeutics that have a chance of success.

Clinical trials are already going full steam ahead. The ADRC serves as a site of several new trials of new antibodies against Alzheimer's pathology, including the A4 Study, DIAN TU, and Biogen's EMERGE. These studies are enrolling people with confirmed amyloid build-up in their brains or individuals at a high genetic risk. "Therapeutics," says Jayadev, "will be more effective if given to the patients in the earliest stages of neurodegeneration."

As new cognitive, imaging, and genetic biomarkers slowly enter into clinical application, it becomes possible to imagine a more hopeful future. In this vision, a person with memory concerns walks into his family clinic and leaves with a guidebook for next



Exome sequencing is the most practical way to identify the genetic culprits in Alzheimer disease. Image credit: National Human Genome Research Institute (NHGRI)

steps forward instead of more questions. A genetically affected family receives a preventive medication tailored just for them. For now, ADRC researchers need to continue improving the predictive potential of brain scans, enrolling research participants, and sequencing exomes. And Giuseppe just has to keep finding those bananas. ■

The ADRC is part of the research consortium of the UW Memory and Brain Wellness Center (MBWC). For news and information about Alzheimer's, Parkinson's, and FTD research, clinical care, and community outreach, visit the MBWC website at depts.washington.edu/mbwc.

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