In the Lab

Study shows body clocks of depressed people are out of sync

Findings give first direct evidence of circadian rhythm changes in depressed brains

DEAD MEN MAY TELL NO TALES, BUT they do tell time. The body's patterns are so regular that time of death can accurately be estimated based on where in their 24-hour cycle the brain's internal clocks happen to stop.

The exception is people with major depression, research led by the U-M Health System recently discovered. Their internal clocks are out of sync.

"It's as if they were living in a different time zone than the one they died in," says Jun Li, Ph.D., an assistant professor in the Department of Human Genetics, who was the lead author of a multi-institution study published in the *Proceedings of the National Academy of Sciences.*

It's well known that people with depression often have trouble sleeping and have altered rapid eye movement (REM) cycles — and, conversely, therapies to help people sleep can alleviate depressive symptoms — but demonstrating how and where the disruption occurs in the brain was a challenging task, says Li, who is also a research assistant professor in the Department of Computational Medicine and Bioinformatics.

Scientists from the U-M, University of California, Weill Cornell Medical College, Hudson Alpha Institute for Biotechnology and Stanford University took material from 89 brains donated shortly after death and paired with extensive clinical information about the individual. Numerous regions of each brain were dissected by hand and with lasers that capture specialized cells, then analyzed to measure gene expression activity. The resulting flood of information was sifted with advanced data-mining tools.

The researchers not only found convincing evidence for the rise and fall in the activity of hundreds of genes that initiate or respond to cycles of behavioral and hormonal activity, they found this cyclical activity in genes where it was previously unknown.

"Hundreds of new genes that are very sensitive to circadian rhythms emerged from this research — not just the primary clock genes that have been studied in animals or cell cultures, but other genes whose activity rises and falls throughout the day," says Huda Akil, Ph.D., co-director of U-M's Molecular and Behavioral Neuroscience Institute and co-site director of the Pritzker Neuropsychiatric Disorders Research Consortium at the U-M. "We were truly able to watch the daily rhythm play out in a symphony of biological activity by studying where the clock had stopped at the time of death. And then, in depressed people, we could see how this was disrupted."

Now, she adds, scientists must use this information to help find new ways to predict depression, fine-tune treatments, and even develop new medications or other types of therapies. One possibility, she notes, could be to identify biomarkers for depression — telltale molecules that can be detected in blood, skin or hair.

Meanwhile, the challenge of determining why the circadian clock is altered in depression still remains. "We

can only glimpse the possibility that the disruption seen in depression may have more than one cause. We need to learn more about whether something in the nature of the clock itself is affected, because if you could fix the clock you might be able to help people get better," says Akil, the Gardner C. Quarton Distinguished Professor of Neurosciences.

—IAN DEMSKY and KARA GAVIN

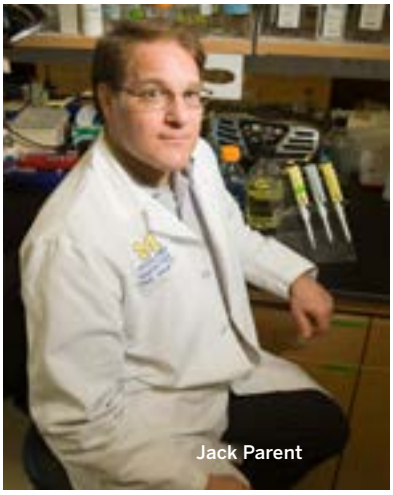
Neurons From Skin Cells

USING THE LATEST ADVANCES IN INDUCED PLURIPOTENT STEM CELL (iPSC) technology, U-M scientists have succeeded in deriving cultured neurons from skin cells removed from epilepsy patients. These neurons provide an important new tool for the study of seizure disorders, allowing scientists to measure signals that neurons in the brain send to one another through tiny portals called sodium channels.

"Using this technique, we can develop and study cells that closely resemble the patient's own brain neurons, without doing a brain biopsy," says research team leader Jack M. Parent, M.D., a U-M professor of neurology and researcher at the VA Ann Arbor Healthcare System.

The neurons were derived from the skin cells of two children with a severe, rare genetic form of epilepsy called Dravet syndrome, as well as from three people without epilepsy. U-M researchers detected abnormally high levels of sodium channel signaling activity in neurons derived from Dravet patients' cells, including spontaneous bursts of communication and "hyperexcitability" that may set off seizures. Neurons made from the skin cells of people without epilepsy showed none of this abnormal activity. "It appears the mutant cells are overcompensating for the reduced number of sodium channels," Parent adds.

The neurons created from people with Dravet syndrome contained a mutation in SCN1A — a gene that encodes an important sodium channel protein. The same mutation is found in most Dravet patients. People born with this mutation have only about half the normal number of sodium channels in their brain neurons.



Jack Parent

SCOTT R. GALVIN, MICHIGAN PHOTOGRAPHY

Many Dravet patients don't respond to current epilepsy medications, giving urgency to the search for new treatment options. The research team plans to screen specific drug compounds for seizure-calming potential in human patients by first testing the drug's impact on neural cells. —KG

MORE ON THE WEB

An Alternative Treatment for Pain

RESEARCHERS FROM U-M AND a major pharmaceutical company have discovered a new approach to treating moderate and severe pain that could pave the way for lower-dose painkillers with fewer side effects.

Many patients with cancer and other chronic health conditions take drugs like morphine, Vicodin and Oxycontin to manage pain. These drugs prevent the perception of pain by binding to molecules called opioid receptors on nerve cells in the brain and spinal cord. The body tends to develop tolerance to these medications, meaning patients must take higher and higher doses for pain relief — increasing the risks of harmful side effects and dependency.

"We have discovered new drug compounds that bind to an alternative and previously unknown site on nerve cell opioid receptors," says Professor of Pharmacology John Traynor, Ph.D. "These compounds have significant potential to enhance a drug's pain-killing action without increasing negative side effects."

If the results are confirmed in research animals and human patients, these novel compounds could be the beginning of a much-needed revolution in the treatment of pain. —BM

MORE ON THE WEB

In the School

Educating Clinical Educators

U-M launches master's degree in health professions education

THE U-M MEDICAL SCHOOL, KNOWN for its top-ranked four-year medical school curriculum and its rigorous Ph.D. programs, is also home to a number of master's degree programs. A new master's program based at the Medical School will help doctors, nurses and other health professionals learn how to educate future members of their professions.

The unique program of individualized learning admitted its first 12 students this fall to work toward master's degrees in Health Professions Education (MHPE). The program focuses on physicians, nurses, pharmacists, dentists and clinical social workers who have or will have responsibility for educating students and early-career trainees. The MHPE program plans to expand to 25 students by its third year.

The program relies heavily on mentor-guided projects that students develop in their own current working environments over the course of two or three years. U-M faculty who specialize in health professions education mentor up to three students closely, ensuring a highly personalized experience.

The Medical School is one of only six institutions in the U.S. that has a department specifically dedicated to medical education, and the U-M is one of few universities with top-ranked schools in a broad range of health disciplines.

Through distance-learning technologies, students will be able to enroll from anywhere — including India, where the U-M is working with the Maharashtra University of the Health Sciences in Nashik on a joint program to educate new health professions educators. Students also come from the U-M itself, which has more than 2,800 faculty members in its health professions schools on the Ann Arbor and Flint campuses.

Larry Gruppen, Ph.D., who led the team that developed the new program, notes that many health professionals who are called upon to lead education and clinical training programs have no formal training in education methods.

"As the number of medical schools and health professions training programs expands, we have to ensure that education programs — and the health professionals they produce — meet the highest standards," says Gruppen, who chairs the Department of Medical Education and serves as the Josiah Macy Jr. Professor of Medical Education. "Our program emphasizes the importance of developing educators who can lead the way in serving national and worldwide needs."

The new master's program teaches students to build and run "competency-based" programs that focus on the practical skills a health provider needs. Programs that train multiple types of health professionals to work with one another, as they will in their careers, receive special emphasis.

Students are expected to publish the results of their work in peer-reviewed journals, ensuring that their experience is shared with other health professions educators — a core value of the program.

The new master's program is the latest in a range of master's degree programs at the Medical School, in addition to the M.D. and Ph.D. programs. Students can also earn master's degrees in biochemistry, bioinformatics, biomedical engineering, clinical research, genetic counseling, health and health care research, human genetics, microbiology, pharmacology or physiology through programs offered by the Medical School — some in partnership with other top-ranked schools across the university. [M]

U-M Clinical Simulation Center

COURTESY OF THE CLINICAL SIMULATION CENTER

Paul DeWolf

U-M Community Mourns Loss of Student

FOURTH-YEAR MEDICAL STUDENT

Paul DeWolf, 25, of Schoolcraft, Michigan, was found dead of a single gunshot wound on July 24, 2013, in his room at the Phi Rho Sigma medical fraternity. After months of investigation, three suspects were arrested in November. Police believe DeWolf was killed during a break-in.

DeWolf, a graduate of Grand Valley State University, also was a U.S. Air Force Second Lieutenant. In a statement at the time of the arrests, the Ann Arbor Police Department, which worked with U-M police officers, the U.S. Marshals Service, the U.S. Air Force Office of Special Investigations and the FBI, said, "There does not appear to be any previous affiliation between the suspects and Paul DeWolf, nor any connection with the University of Michigan or the U.S. Air Force."

At the time of DeWolf's death, the Medical School released a statement that said, in part, "We mourn the passing of a promising and aspiring surgeon who connected quickly with patients, had a thirst for knowledge and a dedication to teamwork, and showed his leadership skills in his academic, military training and athletic pursuits." —RK

Newest Students Face Myriad Changes

THE MEDICAL SCHOOL CLASS OF 2017 WAS FORMALLY WELCOMED IN a White Coat Ceremony held August 4. Composed of 172 slightly older students (six months older than the previous year's average), the class is nearly evenly split between male and female. These newest physicians-to-be will be challenged throughout their careers by advances in medical technologies and changes in the health care environment. Students spent one of their first days of medical school participating in Leadership Day, an orientation exercise that promotes teamwork, leadership and problem-solving. Additional information on the class appears below. —EK

- **Number applying: 5,441**
- **Number interviewed: 578**
- **Students in the class: 172***
- **Class average total GPA: 3.77**
- **Class average MCAT: 34.35**
- **MSTP students (M.D./Ph.D.): 14**

- **Female: 49.4%**
- **Male: 50.6%**
- **Underrepresented in medicine: 28 (16.9%)**
- **Average age: 24.3**

- **Michigan residents: 47.1%**
- **Non-residents: 52.9%**
- **Number of states represented: 33**
- **Total undergraduate institutions represented: 73**
- **Michigan undergraduate institutions represented: 11**

TOP UNDERGRADUATE FIELDS OF STUDY

- **Biology: 26.2%**
- **Natural & Physical Sciences: 18.6%**
- **Engineering: 14.0%**
- **Science (other than biology): 9.3%**
- **Chemistry: 7.0%**
- **Basic Medical Sciences: 5.2%**
- **Biochemistry: 5.2%**

* Data subject to change

White Coat Ceremony 2013

ABOVE: D.C. GOINGS; RIGHT: ERIC BRONSON, MICHIGAN PHOTOGRAPHY

In the Clinic

On-demand Medicine

With 3-D printing technology, U-M doctors and engineers team up to save lives

Kaiba Gionfriddo

BABY KAIBA COULDN'T BREATHE. The walls of his airway were weak and kept collapsing. He had to be resuscitated daily. At 2-months-old he was put on a ventilator. There was nothing Kaiba's parents April and Bryan Gionfriddo could do for their son but keep a vigil and send up their prayers.

"Quite a few doctors said he had a good chance of not leaving the hospital alive," April recalls.

Kaiba's doctor in Ohio reached out to the University of Michigan, where physicians and engineers had been working together to develop an implantable plastic splint that the body can absorb over time, and that can be tailored from CT scan-data to exactly fit each patient.

Glenn Green (M.D. 1991), associate professor of pediatric otolaryngology, and his colleague, Scott Hollister, Ph.D., professor of biomedical engineering and mechanical engineering, thought the new device might be able to save Kaiba's life. They obtained emergency clearance from the federal Food and Drug Administration to try the technique, which uses a bioplastic known as polycaprolactone.

"Even with the best treatments available, Kaiba had continued to have these episodes," Green says. "Without help, he was going to die."

On February 9, 2012, Kaiba underwent surgery at C.S. Mott Children's Hospital. The splint was sewn around Kaiba's airway to expand one of the major air passages off his windpipe and give it a rigid skeleton to aid future growth.

"It was amazing. As soon as the splint was put in, the lungs started going up and down for the first time and we knew he was going to be okay," says Green.

Three weeks after the procedure Kaiba was taken off ventilator support and has not had breathing trouble since. The first-of-its-kind case was featured in *The New England Journal of Medicine*.

"The material we used is a nice choice for this — it takes about two to three years for the trachea to remodel and grow into a healthy state, and that's about how long this material will take to dissolve into the body," says Hollister, who is also an associate professor of surgery. "Kaiba's case is definitely the highlight of my career so far. To actually build something that a surgeon can use to save a person's life? It's a tremendous feeling."

The technique goes beyond infant airways — 3-D printing technology and biomaterials are seen as the wave of the future for building and reconstructing a variety of tissues — such as noses, ears, and bones in the face and spine.

Meanwhile, they also offer new hope to patients, like Kaiba, born with severe tracheobronchomalacia. About one in 2,200 babies are born with the disorder, but few cases are as severe as Kaiba's.

"Severe tracheobronchomalacia has been a condition that has bothered me for years," says Green. "I've seen too many children die from it. To see this device work — it's a major accomplishment and offers hope for these children."

Kaiba, now 2, is still doing well. Since the technique was published, the case has garnered national media attention and in July the family appeared on the "Today" show.

"He has not had another episode of turning blue," April Gionfriddo says. "We are so thankful that something could be done for him. It means the world to us."

—IAN DEMSKY and MARY MASSON

COURTESY OF THE GIONFRIDDO FAMILY

Inside the Dying Brain

HOW LONG DOES THE BRAIN STAY active after the heart stops beating? Apparently, longer than many scientists thought. A U-M study of electrical activity in the brains of rats during and after clinical death found that high levels of electrical activity continued even after the animals' hearts stopped beating and blood stopped flowing to the brain. These brain activity patterns were widespread, highly synchronized and similar to those measured during conscious activity.

"This study, performed in animals, is the first to show what happens to the neurophysiological state of the dying brain," says lead study author Jimo Borjigin, Ph.D., associate professor of molecular and integrative physiology and associate professor of neurology."Our study will form the foundation for future research to investigate mental experiences occurring in the dying human brain, including reports of seeing light and other near-death experiences during cardiac arrest." —SK

MORE ON THE WEB

LEFT: DREAMSTIME.COM
RIGHT: ERIC BRONSON, MICHIGAN PHOTOGRAPHY

U-M to Offer Retinal Implants

KELLOGG EYE CENTER is one of 13 centers nationwide selected to offer a new FDA-approved retinal implant that could provide partial sight for individuals with late-stage retinitis pigmentosa (RP). RP is an inherited retinal degenerative disease that causes progressive vision loss and eventual near-blindness due to a gradual loss of light-sensitive retinal cells called rods and cones.

Thiran Jayasundera

"Until now, we've had no treatment options for patients with advanced RP," says Thiran Jayasundera, M.D. (Fellowship 2009), an assistant professor of ophthalmology and visual sciences at the U-M. "Clinical studies have shown that the Argus II System can bring light back into a patient's world — allowing them to detect shapes of people and objects, gain more independence and go about their daily lives with more confidence."

The prosthesis is surgically implanted in one eye and individuals wear glasses equipped with a camera that captures images and converts them into a series of small electrical pulses. The pulses are transmitted wirelessly to the prosthesis and its array of electrodes on the surface of the retina. These pulses are intended to stimulate the retina's remaining cells, resulting in the corresponding perception of patterns of light in the brain. By learning how to interpret these visual patterns, people with RP can regain some visual function.

Sometimes called an artificial retina or "bionic eye," the Argus II Retinal Prosthesis System was developed by a California-based company called Second Sight Medical Products, Inc., and was approved for use in U.S. patients by the Food and Drug Administration in February 2013. —BN

MORE ON THE WEB

In the Clinic

Healing ACLs

OFTEN DUBBED AN ATHLETE'S WORST NIGHT-mare, a tear in the anterior cruciate ligament, or ACL, usually requires surgical repair, months of intense rehabilitation and a long break from any sports-related activity. In spite of improved ACL recovery therapies, most patients will have muscle weakness or atrophy after the injury that can be a career-killer in sports and ultimately develop into osteoarthritis, says Christopher Mendias (Ph.D. 2007), an athletic trainer and a U-M assistant professor of orthopaedic surgery and of molecular and integrative physiology.


Christopher Mendias

Mendias directed a U-M study that identified a new potential drug target — a hormone called myostatin, which appears to play a key role in causing muscle damage after an ACL tear. Myostatin has shown promise as a potential drug target for other conditions such as muscular dystrophy and cancer, and blocking the protein has led to increased muscle mass and strength.

"This is the first study in humans that opens the door to a potential therapy to prevent muscle atrophy," says Mendias. "We see it as an important step in restoring athletic and functional abilities in the short term, and in preventing osteoarthritis in the long term." —BM

MORE ON THE WEB

Help for the Caregiver

SOMETIMES THE MOST DIFFICULT PART OF CARING for loved ones with dementia is their disruptive behavior changes. With no reliable medications and limited information available to family caregivers, dementia-related behavior changes are a common source of stress — often resulting in a nursing home placement.

With a $1.7-million grant from the National Institutes of Health (National Institute of Nursing Research), researchers from the U-M and Johns Hopkins University will work together to design a web-based tool called WeCare to help caregivers track, understand and treat dementia's behavioral symptoms.

Helen Kales, M.D. (Residencies 1997 and 1998), a U-M associate professor of psychiatry and researcher at the VA Ann Arbor Healthcare System, and her collaborator, Laura Gitlin, Ph.D., Director of the Center for Innovative Care in Aging at Johns Hopkins University School of Nursing will direct the project. —JH

MORE ON THE WEB

Health Briefs

Pertussis, often called whooping cough, can be deadly for infants too young to be vaccinated, and outbreaks of this highly infectious disease are becoming more common in the U.S. Effective Tdap vaccines are available, but most people receive them during childhood and protection wears off over time. A recent C.S. Mott Children's Hospital National Poll on Children's Health found that only 20 percent of adults surveyed had been vaccinated within the past 10 years. To avoid exposing vulnerable babies to the disease, pediatricians recommend that all teens and adults who will be around a newborn get a booster shot.

MORE ON THE WEB

Rates of severe depression in older Americans declined between 1998 and 2008, according to a U-M Health System study — especially among people aged 80 to 84 who are considered to be at high-risk for depression. During the same decade, however, rates of depression increased in adults aged 55 to 59, a group not traditionally considered to have a high-risk of developing the disease. U-M researchers will continue the study to determine why depression is becoming more common in late middle-age.

MORE ON THE WEB