MICE SLEEPING FITFULLY PROVIDE CLUES TO INSOMNIA

GENETICALLY ENGINEERED MICE MIMIC COMMON SLEEP PROBLEMS

Mice that sleep fitfully could help researchers unravel the mystery of insomnia.

Researchers at Washington University School of Medicine in St. Louis studied mice genetically modified to mimic the genetic disease neurofibromatosis type 1 (NF1), which is associated with sleep problems. They found that the animals, like some people with NF1, slept in short, irregular spurts. Studying these mice could help identify the molecular and cellular mechanisms that go awry and cause fragmented sleep patterns in people with and without the disease, the researchers said.

“The mice are a tool for us to understand how sleep disturbances arise and how sleep disruption contributes to problems with learning and attention;” said David H. Gutmann, MD, PhD, the Donald O. Schnuck Family Professor of Neurology and the study’s senior author. “This could apply both to people with NF1 and others without NF1 who also have sleep problems.”

The findings were published Jan. 4 in the Journal of Sleep Research.

As many as half of people with NF1 – a condition that causes benign tumors in the brain and on nerves throughout the body – have difficulty falling or staying asleep. Learning disabilities and attention problems also are common in children with NF1, and both may be exacerbated by poor sleep. But doctors don’t know why some children with NF1 develop sleep problems and others don’t, nor can they do much to help them sleep better.

“Right now we just treat children and adults with NF1 and sleep problems like we treat patients without NF1 because we don’t understand what causes them,” said Gutmann, who also directs the Neurofibromatosis Center at Washington University.

Co-first author Corina Anastasaki, PhD, an instructor in Neurology, bred mice with a mutation in their Nf1 gene similar to what is seen in people with NF1. Then, co-first author Nicholas Rensing and Michael J. Wong, MD, PhD, the Allen P. and Josephine B. Green Professor of Pediatric Neurology, fitted the mice miniature versions of the caps people wear for sleep studies, enabling them to measure brain waves and identify sleep patterns.

Mice normally sleep during the day and, like people, cycle several times from deep, dreamless sleep to REM sleep – or dreaming – and back again. Mice with an Nf1 mutation, however, tended to wake up soon after they entered deep sleep. The result was a fragmented, and probably not restful, day of sleep.

“Throughout the whole night and day, they fell asleep and woke up when they shouldn’t have,” Anastasaki said. “They fell into deep sleep, but they didn’t stay there.”

Although the mice were engineered to mimic human NF1 disease, they could yield insights about the biological underpinnings of sleep in general, which could help people with sleep problems unrelated to NF1. About a third of American adults report some degree of insomnia, and 15 percent have chronic insomnia that lasts three months or more.

“It is hard to study sleep problems in people because there are so many factors that influence how well you sleep – maybe you’re stressed out, maybe you’re sick, maybe you’re taking care of a new baby,” Gutmann said. “But now we have a controlled system that we can use to start looking at which cells and proteins are involved, and which biological factors influence sleep quality. Only when we understand the problem better will we be able to find better ways to treat it.”

This article originally appeared in the Washington University School of Medicine News Hub on January 7, 2019.
PATIENT SPOTLIGHT: PHILLIP

I’m often asked what brought us to St. Louis, since neither my husband nor I have family in the area. A promising job offer in 2000 prompted us to move from North Dakota, but it wasn’t until years later that I would come to realize our move was “meant to be” for an entirely different reason.

Our son, Phillip, was born in 2003. At his six month exam, our pediatrician noticed several birth marks on his torso, which led to a referral to Dr. David Gutmann at St. Louis Children’s Hospital. We would learn that these birthmarks were actually café-au-lait spots and one indicator of Neurofibromatosis Type 1 (NF1). Phillip was five years old when a second indicator, Lisch nodules on the iris of his eyes, was found, and the diagnosis of NF1 was confirmed. People with NF1 are at risk for developing tumors throughout their bodies. Naturally, we were scared and confused about what this meant for our child’s future.

Dr. Gutmann was wonderful, and he patiently answered our questions, as well as assured us that Phillip was capable of leading a normal, productive life. He introduced us to his team of specialists at St. Louis Children’s Hospital and the powerful network of support they provide: physical therapy, occupational therapy, speech pathology, pediatric neuropsychology, orthopedic surgery, and ophthalmology—a group of talented and caring professionals that we’ve utilized over the years.

Another support that has been beneficial to our family is Club NF, offered through the Washington University NF Center. Phillip was six years old when we first attended a Club NF activity, and he loved it immediately. As he’s grown older, these free activities have allowed him to learn and practice social and motor skills by swimming, ice-skating, cooking, playing chess, dancing, painting, wall-climbing, animal encounters at the zoo, learning about dinosaur digs at the Science Center, and even yoga surfing! While the kids play and interact, parents have the opportunity to hear from various speakers and enjoy making friendships, as well. Questions from parents may vary from educational (IEP, 504, technology), emotional, social, and behavioral, and the Washington University NF Center staff does a fantastic job finding the right speakers to address these concerns.

Fast forward to 2019... Phillip is now 15 and a typical teenager with his driver’s permit, cell phone, and love of gaming. A sophomore in high school, he’s an honor student, enjoys golf and weight conditioning, plays piano, and works to perfect his German. NF1 does not limit him. He now participates in Teen NF, which provides a friendship group that understands and accepts him because they are going through the same journey. Knowing that there are other teens with NF1 has helped him be comfortable with his diagnosis. He now enjoys volunteering at Club NF and taking on a mentor role for the younger kids.

I do believe our move to St. Louis was “meant to be” and we were guided here to have access to St. Louis Children’s Hospital and Dr. Gutmann and his team of specialists at the NF Clinic. We will be forever thankful for the dedication and compassion they show for their NF patients and continued research.

– written by Suzy Effertz
COLLABORATIVE RESEARCH TEAM DEVELOPS PIG MODEL OF NF1 OPTIC GLIOMA

Children and adults with NF1 can develop a wide variety of clinical features, including brain and nerve tumors. While small animal models of NF1 have been successfully generated in flies and mice, none of these animals display the spectrum of clinical problems found in people with NF1.

Spearheaded by Dr. Adrienne Watson of RecombineX, Inc. and Dr. David Largaespada at the University of Minnesota, a novel swine model of NF1 was recently developed. These minipigs exhibit many of the clinical hallmarks of NF1, including café au lait macules, neurofibromas, and optic pathway glioma. In contrast to previously reported Nf1 mouse models, these animals spontaneously develop these features, similar to people with NF1. In this regard, this minipig platform provides an unprecedented opportunity to study the complex biology and natural history of NF1. Moreover, deployment of these NF1 swine could prove indispensable for the development of advanced imaging methods and disease biomarkers, as well as the evaluation of future NF1 targeted therapies.

This work was published in Communications Biology.
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SITEMAN CANCER CENTER HONORS ROCK DOCS

Each year Siteman Cancer Center sponsors CUREiosity, an event to celebrate the “Rock Docs” making a difference at the Alvin J Siteman Cancer Center as well as the cutting edge “Rock Star Research” being conducted at the institution. This past year more than 300 guests were in attendance, and one of our very own NF Center researchers, Dr. Angela Hirbe, was named a 2018 Rock Doc. Dr. Hirbe is an Assistant Professor in the Division of Oncology, and her research focuses on identification of biomarkers and therapeutic targets for malignant peripheral nerve sheath tumors (MPNSTs), aggressive soft tissue sarcomas that occur at an increased frequency in patients with Neurofibromatosis Type 1 (NF1). Congratulations to Dr. Hirbe and all of the 2018 Rock Docs!

INTERNATIONAL NF TEAM DISCOVERS NEW MARKERS FOR MICROGLIA

Monocytes/macrophages are immune system-like cells important for normal brain function. In the healthy brain, resident microglia are the major macrophage cell population; however, in brain tumors, peripheral monocytes/macrophages can infiltrate the brain and participate in brain tumor growth. Distinguishing these two populations is often challenging, owing to a paucity of universally accepted and reliable markers.

To identify discriminatory marker sets for microglia and peripheral monocytes/macrophages, Verena Haage, a graduate student in the laboratory of Dr. Helmut Kettenmann, employed a large meta-analytic approach. This project was performed in collaboration with Dr. David H. Gutmann, Director of the Washington University NF Center. Using this approach, they discovered a robust set of microglia and peripheral monocyte/macrophage expression markers to discriminate these monocyte populations in both health and disease.

This report was published in Acta Neuropathologica Communications.
NICOLE’S NOOK: C-PEN READER

In addition to the multitude of apps, extensions and built-in features that can aid in reading, there are also other stand-alone devices available. Recently, I trialed the C-Pen Reader by Scanning Pens. This lightweight “pen” is slightly larger in size than a highlighter. It features optimal character recognition that scans printed text and reads it aloud. This device is especially beneficial to those who struggle with reading or comprehension, or those that use English as their second language.

While schools are progressing with technology, many are not entirely digital. For that reason, a reading pen can be a powerful device in that setting. Worksheets, paper and exams are still frequently utilized. A reading pen can allow students to work independently, scanning the text themselves. This has the potential to eliminate the need for an aide or paraprofessional, as well as reduce the amount of teacher preparation as students can access any of the printed material in class. The reading pen also can be used with earbuds or headphones, preventing any distraction to others and promoting inclusion in the general education setting.

The reader pen functions not only as a text reader, but also as a dictionary and as a recorder for quick notes or reminders. You can scan to file by connecting to a computer to allow for greater storage. Also available is the Exam Reader pen which allows students to read test questions to themselves. This pen features an exam lock to which it becomes a read-only device. It cannot access the dictionary or record. Exam Reader pens can be used for tests, even college board exams, so long as the accommodation of text-to-speech or portable speech is written in your student’s IEP.

Many of your state lending libraries feature these pens to trial to see if it may help your student. I highly recommend doing a little research to see if such a device would help your student become more efficient and independent!

Nicole Weckherlin, OTR/L Occupational Therapist

UPCOMING EVENTS

CLUB NF - PLAYS BOARD GAMES - AUGUST 3, 2019
BEAT NF - FALL 2019 - OCTOBER 2019
CLUB NF - GOES TO THE ZOO - OCTOBER 5, 2019

For more details, or to RSVP, please visit our events website at: https://nfcenter.wustl.edu/events/