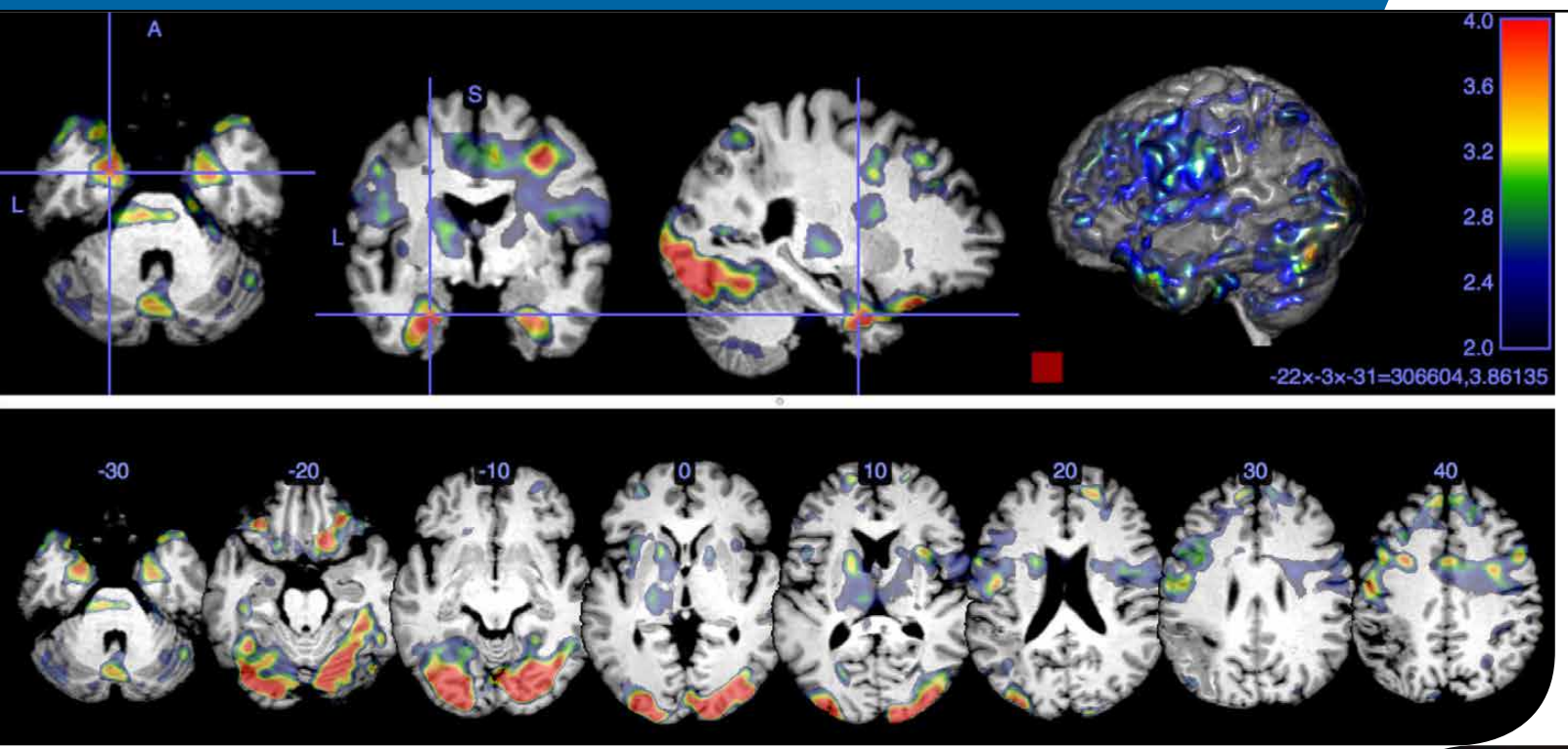
JOHNS HOPKINS
NeuroLogic

NEWS FOR PHYSICIANS FROM THE JOHNS HOPKINS DEPARTMENTS OF NEUROLOGY AND NEUROSURGERY

WINTER 2016

JOHNS HOPKINS MEDICINE



Johns Hopkins researchers are studying transcranial direct-current stimulation (TDCS) to augment language therapy after stroke.

Pictured: areas of brain activation during an overt picture-naming task (compared to rest) in a patient with a left hemisphere stroke (primarily in the parietal cortex), used to localize the area of stimulation for TDCS during language therapy. Areas significantly activated include bilateral visual processing areas in the occipital lobes as well as in the left temporal cortex—important for language comprehension—and in in the left posterior frontal cortex—critical for articulation of speech.

Stimulating Communication in Aphasia Patients

Before **Argye Hillis** was a Johns Hopkins neurologist, she was a speech-language pathologist. Many of her patients were trying to recover from aphasia, the communication disorder caused mainly by stroke and characterized by difficulty producing or comprehending speech or written language.

"It's a problem that I've been interested in a long time," she says.

The most common treatment for aphasia is language therapy delivered by a speech-language pathologist that's augmented largely by computer-based programs at home. However, Hillis says, this therapy has limited effectiveness—patients who receive it often continue to have debilitating language problems that persist for years or become permanent.

That's why Hillis and colleagues at Johns Hopkins, the University of South Carolina (USC) and the University of California, Irvine (UCI), recently launched a multisite effort known as the Center for the Study of Aphasia Recovery (C-STAR) to better understand aphasia and develop new ways to treat this condition. C-STAR is funded by an $11.1 million grant from the National Institutes of Health over five years.

Hillis, who serves as the principal investigator of C-STAR's clinical core, is leading a study at Johns Hopkins to investigate the use of transcranial direct-current stimulation (TDCS) to augment language therapy. In this approach, electrodes placed on the scalp deliver a constant, low current to the brain.

The theory behind TDCS suggests that, when delivered while subjects perform a task, the current changes threshold of activation that neurons involved in the task need to fire. Over time, this lower threshold leads to neuroplasticity, with new neurons taking over the functions of those damaged during stroke.

The researchers will compare those who receive this additional intervention during language therapy to those who receive conventional language therapy alone, enrolling only patients who've had strokes within three months. They'll compare results to a similar study

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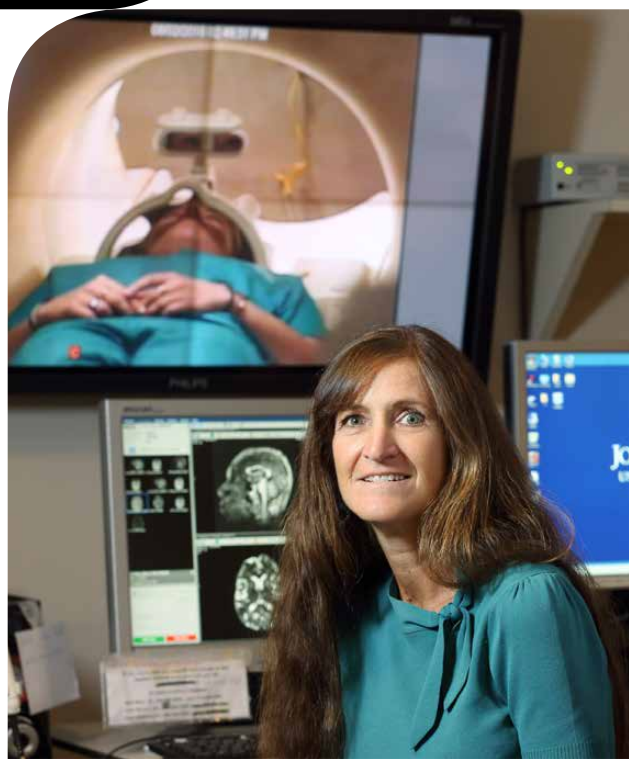

"OUR ULTIMATE HOPE IS THAT WE FIND SOMETHING THAT CAN REALLY IMPROVE APHASIA RECOVERY AND GIVE PATIENTS THE ABILITY TO COMMUNICATE EFFECTIVELY AGAIN."

ARGYE HILLIS

SPINE

The Spine Program's **New Director**

Nicholas Theodore's research focuses on spinal cord injury—extending from the genetics of spine disorders to robotic tools to improve surgery.

LIKE MANY NEUROSURGEONS, **Nicholas Theodore** says that it's the intriguing anatomy of the brain that drew him into the specialty. But, during his residency, the spine caught his interest and has held it ever since. Now the new director of the Johns Hopkins Neurosurgical Spine Program, Theodore adds that it's the incredible outcomes of spine surgery that have kept him fulfilled over decades of practice. For the patients he cares for, which include all ages with conditions including trauma, infections, fractures, herniated discs, degeneration and stenosis, he notes that spine surgery frequently has the possibility of completely resolving their complaints.

"Through surgery," he says, "we can often completely cure a patient's spine problem and get them back to fully living their lives."

It's also a subspecialty in which many of the encompassed conditions stand poised for a revolution in care. Much of Theodore's research focuses on spinal cord injury, a devastating problem that still largely remains an enigma. By gaining a better understanding of this mysterious condition, he and his colleagues are striving to improve outcomes.

In one ongoing project, started in Theodore's former position as director of spinal neurosurgery at the Barrow Neurological Institute in Phoenix, Arizona, and continuing at Johns Hopkins, Theodore and his colleagues are studying how to get the greatest blood flow to the spinal cord after an acute injury. Rather than raise a patient's blood pressure, the current standard of care, the team's work suggested that draining spinal fluid to decrease pressure instead brought more blood to the spinal cord. Based on these findings, they recently launched a three-year, multisite trial funded by the Department of Defense to evaluate this intervention in human patients.

Theodore's research also extends from the genetics of spine disorders to robotic tools to improve surgeries. He's currently working on a robot that can precisely place screws in a patient's spine at the touch of a screen displaying their anatomy.

"THROUGH SURGERY, WE CAN OFTEN COMPLETELY CURE A PATIENT'S SPINE PROBLEM AND GET THEM BACK TO FULLY LIVING THEIR LIVES."
NICHOLAS THEODORE

On a more operational level, Theodore is working to improve the field overall by improving patients' experiences. In his new role, he plans on working to streamline care at the Johns Hopkins Spine Center by coordinating it among multiple specialists who take care of spine patients. By making the center a "one-stop shop," he says, patients will receive better care while also saving time and effort.

"Dr. Theodore is not only a phenomenal physician and extraordinary surgeon; he's also wonderfully compassionate," says **Henry Brem**, director of the Johns Hopkins Department of Neurosurgery. "He doesn't just take patients into surgery but really takes care of them." ■

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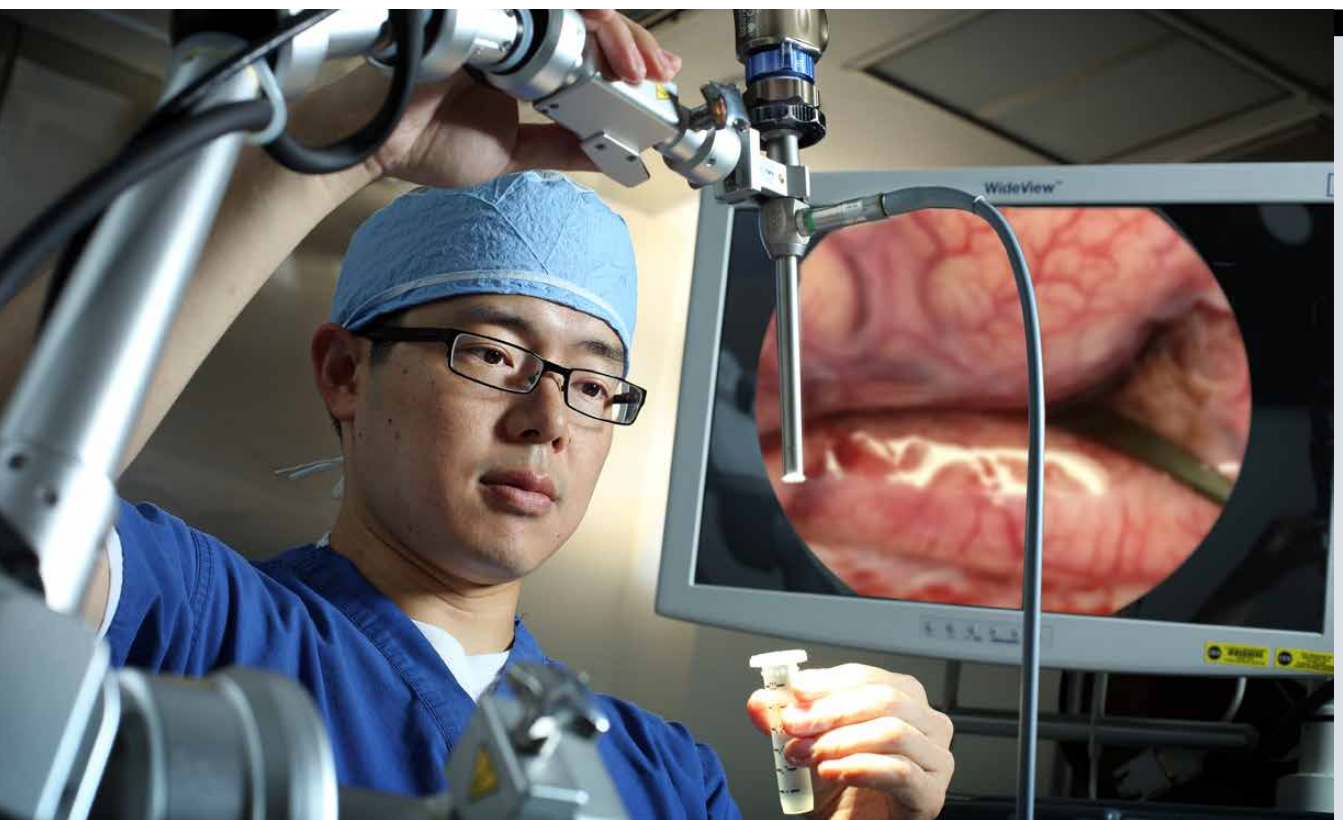


Sparing patients open craniotomies, neurosurgeon Kaisorn Chaichana uses the minimally invasive tubular retractor to reach deep seated lesions within the brain.

BRAIN SURGERY

A New Way **into t**

THE TRADITIONAL WAY TO REACH A DEEP-seated lesion within the brain is through an open craniotomy. While this route is effective at accomplishing the primary goal of accessing the tumor, it's littered with collateral damage, says Johns Hopkins neurosurgeon **Kaisorn Chaichana**.

"It usually requires a big incision, a big opening in the skull, a big opening in the dura," he says. "As we dissect downward, we're compromising the white matter the whole time." The end result, he adds, is substan-

Studying **Sleep Drive** in Flies

WHY HUMANS AND OTHER ANIMALS sleep when we do has long been a mystery—an enigma that's hampered finding ways to treat sleep disorders. To help solve this puzzle, Johns Hopkins neurologist **Mark Wu**, who treats patients with sleep disorders in the clinic and studies these problems in the lab, turned to the quintessential biological model: the fruit fly.

Searching for sleep-regulating cells in the insects' brains, Wu's team used genetic engineering to turn on small numbers of neurons in more than 500 *Drosophila* strains. They then measured how these flies slept when these neurons fired. Several strains continued to sleep for hours even after they turned off the neurons, suggesting that the researchers triggered sleep drive in these flies, which led to the persistent sleepiness.

Using fluorescent microscopy, the scientists then examined the fly brains to specifically pinpoint the identity and location of the sleep drive-inducing cells, which were genetically engineered to glow green. They were found in a structure called the ellipsoid body.

To further confirm that they'd found the right cells, the researchers blocked the neurons from firing by genetically engineering them to make tetanus toxin, which silenced the cells. The flies with the silenced neurons slept on their normal schedule, but when they were deprived of sleep during the night by mechanically shaking their vial houses, they got about 66 percent less "rebound sleep" compared to control flies, suggesting that they felt less sleepy after sleep deprivation.

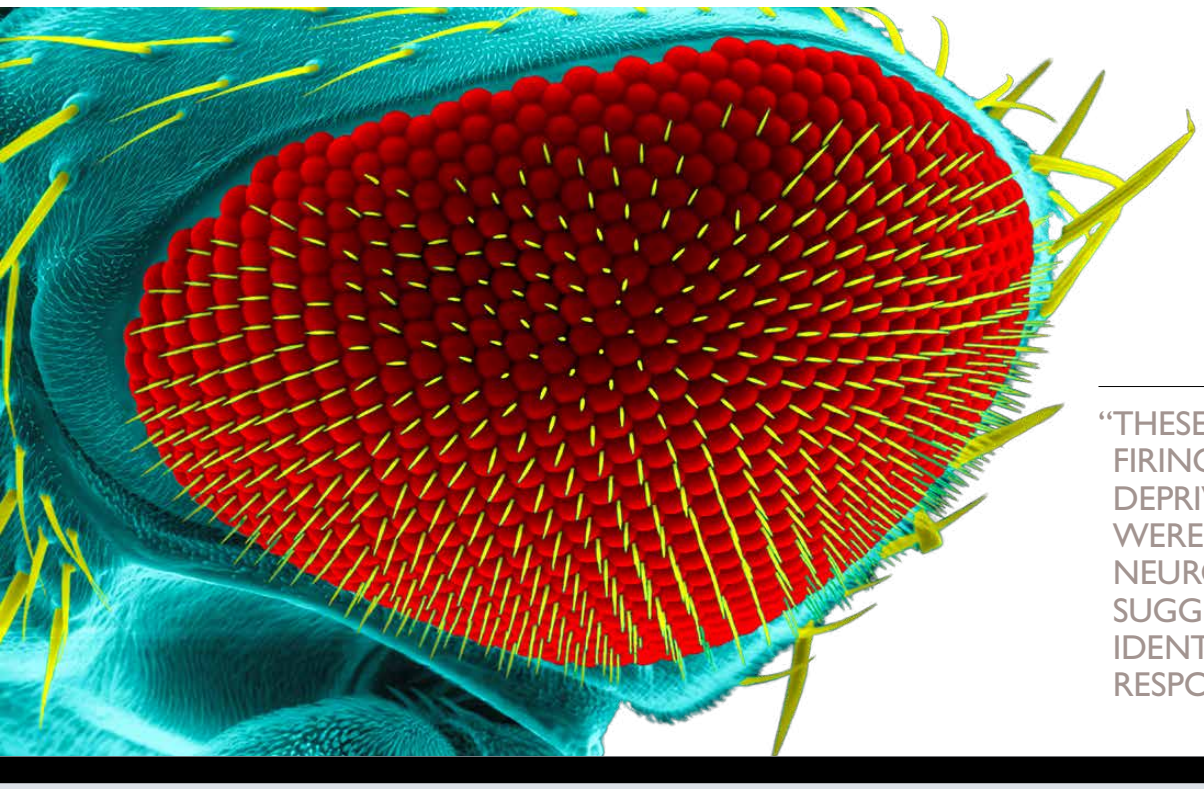
Next, the researchers tested how these special neurons behaved on their own in awake, sleeping or sleep-deprived fruit flies. They used tiny electrodes to measure the firing of these cells in well-rested, awake fruit flies, in fruit flies that were an hour into their sleep cycle, and in fruit flies after 12 hours of sleep deprivation.

In the well-rested fruit flies, the neurons fired only about once per second and were the least active. In the sleeping fruit flies, the neurons fired almost four times a second. In the sleep-deprived fruit flies, the neurons were the most active, firing at about seven times per second.

"These neurons have higher firing rates the more sleep-deprived the fruit flies were and firing of these neurons puts flies to sleep, suggesting that we've identified the key cells responsible for sleep drive," says Wu.

Further investigation by Wu's team suggests that sites on the neurons' surfaces that release sleep-promoting neurotransmitters increase in size and number when the flies are sleep-deprived, allowing a flexible system for triggering sleep when the insects most need rest.

"Figuring out how sleep drive works should help us one day figure out how to treat people who have an overactive sleep drive that causes them to be sleepy all the time and is resistant to current therapies," Wu says. ■



"THESE NEURONS HAVE HIGHER FIRING RATES THE MORE SLEEP-DEPRIVED THE FRUIT FLIES WERE AND FIRING OF THESE NEURONS PUTS FLIES TO SLEEP, SUGGESTING THAT WE'VE IDENTIFIED THE KEY CELLS RESPONSIBLE FOR SLEEP DRIVE."
MARK WU

the Brain

tial blood loss, long hospital stays, long recovery times and an increased risk of damage to brain structures, which can cause neurological deficits.

Enter the minimally invasive tubular retractor, a device that Chaichana has recently incorporated into many of the procedures he's performed to help mitigate these issues. With a tubular diameter slightly less than a nickel, this retractor allows for less invasive brain surgery by using an obturator with an atraumatic tip to push white matter away instead of cutting it.

During procedures that use this device, Chaichana and his colleagues typically rely on MRI with diffusion tensor imaging data gathered before surgery to guide an interoperative navigation system. Using these data to pinpoint the location of a lesion, the surgeons make a small opening about the size of a silver dollar through the scalp, skull and dura. They then insert the tubular retractor between white matter tracts directly over the tumor.

Once the obdurator is in place, the surgeons can remove an inner metal insert, leaving behind an inner clear sheath. The surgery is performed with an exoscope—a small camera that hovers over the surgical field—and tools to go within the device. Using this protocol, Chaichana and his colleagues can resect entire tumors with minimal disruption to the surrounding brain structures.

This approach is particularly valuable for tumors in eloquent locations, Chaichana says. Treating these tumors using traditional surgical methods would increase the result in motor, language or visual field deficits because of the large dissection of the critical brain matter. However, in the 30 cases he's already treated using this device over the past year, these functions have been largely preserved. These patients have also had shorter surgeries, significantly less blood loss, shorter hospital stays and quicker recoveries, he adds.

Because of its host of benefits, Chaichana says, he expects that use of this device will grow throughout this field over time.

"With this approach, we can offer patients the same great results as an open resection," he says, "while also giving them a much greater chance of preserving their neurological function and quality of life." ■

Refer a patient: 410-955-6406

Stimulating Communication in Aphasia Patients

(continued from page 1)

currently taking place at USC for patients whose strokes occurred longer ago.

Hillis' team will also study the interaction of these treatments with selective serotonin reuptake inhibitors (SSRIs), a class of drugs typically used to treat depression and often prescribed to patients following stroke. Because some evidence suggests that SSRIs can aid post-stroke motor recovery, Hillis and her colleagues are looking to see if these drugs can give language therapy a similar boost, particularly when combined with TDCS.

These efforts will be combined with imaging and theoretical studies taking place at USC and UCI. Together, Hillis says, the study will attack the problem of aphasia from multiple angles.

"Our ultimate hope," she says, "is that we find something that can really improve aphasia recovery and give patients the ability to communicate effectively again." ■

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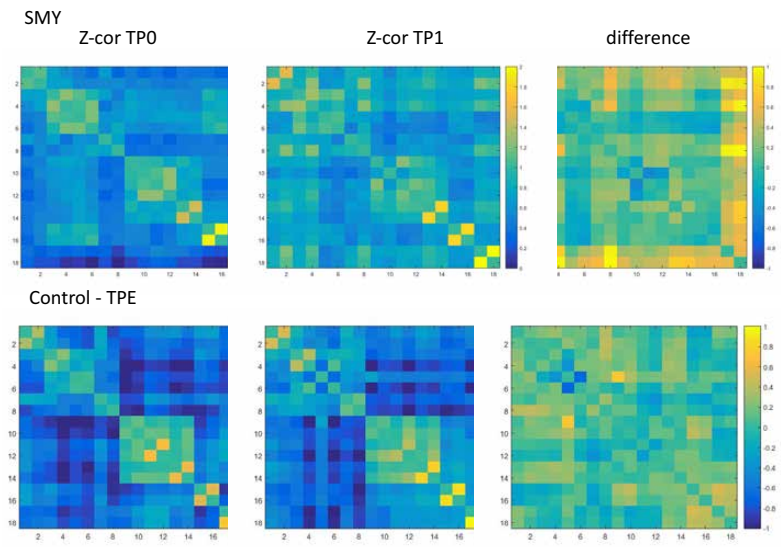

The top row shows resting state functional connectivity matrices (from resting state functional MRI) before TDCS plus language therapy (time point 0, or TP0, on left) and after TDCS plus language therapy (time point 1, or TP1, middle), and a matric showing change in connectivity from TP0 to TP1, pre- to post-treatment. There is a widespread increase in connectivity in the patient post-treatment, but it is most significant between right cerebellum (last row and columns) and other cortical areas. The patient had TDCS to right cerebellum in this study of TDCS plus language therapy (Rajani Sebastian, Ph.D., primary investigator).

The bottom row shows the same connectivity matrices at each time point and the difference (right matrix) in an age-matched control who had resting state MRI at the same time points as the patient. There was no significant change in connectivity in the control over time.

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Inside