Irregular Sleep Schedules Linked to Bad Moods and Depression

An irregular sleep schedule can increase a person's risk of depression over the long term as much as getting fewer hours of sleep overall, or staying up late most nights, a new study suggests. Even when it comes to just their mood the next day, people whose waking time varies from day to day may find themselves in as much of a foul mood as those who stayed up extra late the night before, or got up extra early that morning, the study shows.

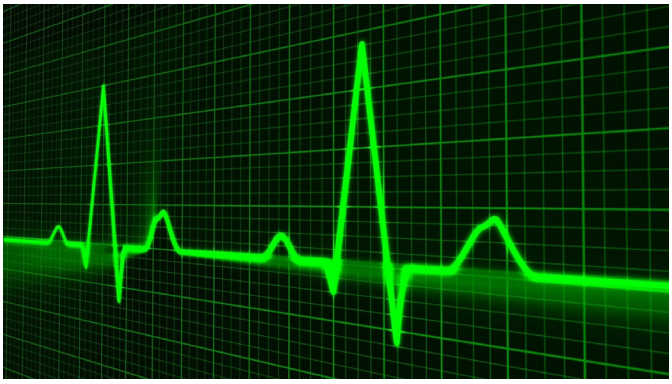
The study, conducted by a team from Michigan Medicine used data from direct measurements of the sleep and mood of more than 2,100 early-career physicians over one year. It has been published in *npj Digital Medicine.*

The new paper is based on data gathered by tracking the interns' sleep and other activity through commercial devices worn on their wrists and asking them to report their daily mood on a smartphone app and take quarterly tests for signs of depression. Those whose devices showed they had variable sleep schedules were more likely to score higher on standardized depression symptom questionnaires, and to have lower daily mood ratings. Those who regularly stayed up late, or got the fewest hours of sleep, also scored higher on depression symptoms and lower on daily mood.

"These findings highlight sleep consistency as an underappreciated factor to target in depression and wellness," says Cathy Goldstein, M.D., M.S., an associate professor of neurology and physician in the Sleep Disorders Center at Michigan Medicine.

Heartbeat Secrets Unlocked As Cardiac Rhythm Gene Role Identified

The University of Melbourne study found that mutation of the gene, Tmem161b, causes potentially fatal cardiac arrhythmia. The findings have been published in *Proceedings of the National Academy of Sciences (PNAS).*



University of Melbourne Associate Professor Kelly Smith said the research discovered the function of Tmem161b. "Zebrafish eggs were used as they have complex beating hearts, similar to humans," Associate Professor Smith said. "Eighty percent of zebrafish genes are like ours and both use the same basic 'equipment'." The researchers used naturally produced eggs to observe organ development under a microscope. The eggs are translucent, which allowed observation without interference. Associate Professor Smith said this important discovery would improve our knowledge of the heartbeat. "What's important is, it describes a new gene in cardiac rhythm, which helps us to understand the fundamentals of what it takes to make a heartbeat," Associate Professor Smith said.

"We screened thousands of zebrafish families and found one with inherited arrhythmia. Working backward from there, we found which gene was mutated to cause the arrhythmia. It turned out to be a completely uncharacterized gene." Associate Professor Smith said she suspected the finding would be relevant in humans. "Given the prevalence of cardiac arrhythmia, the more we know about how the heart works, the better," she said. "The gene described in the research appears to play a central function, so we expect it to be important in more than just controlling heart rhythm.

Caffeine Consumption Found to Alter Brain Structure

Researchers from the University of Basel have shown in a study that regular caffeine intake can change the gray matter of the brain. However, the effect appears to be temporary. Caffeine can disrupt sleep if consumed in the evening. Sleep deprivation can in turn affect the gray matter of the brain. So can regular caffeine consumption affect brain structure due to poor sleep? A research team led by Dr. Carolin Reichert and Professor Christian Cajochen of the University of Basel and UPK (the Psychiatric Hospital of the University of Basel) investigated this question in a study. The results showed that the caffeine consumed as part of the study did not result in poor sleep. However, the researchers observed changes in the gray matter in the journal *Cerebral Cortex*.

A group of 20 healthy young individuals, all of whom regularly drink coffee daily, took part in the study. They were given tablets to take over two 10-day periods and were asked not to consume any other caffeine during this time. During one study period, they received tablets with caffeine; in the other, tablets with no active ingredient (placebo). At the end of each 10 days, the researchers examined the volume of the subjects' gray matter through brain scans. They also investigated the participants' sleep quality in the sleep laboratory by recording the electrical activity of the brain (EEG). Data comparison revealed that the participants' depth of sleep was equal, regardless of whether they had taken the caffeine or the placebo capsules. But they saw a significant difference in the gray matter, depending on whether the subject had received caffeine or the placebo. After 10 days of placebo, the volume of gray matter was greater than following the same period with caffeine capsules.

The difference was particularly seen in the right medial temporal lobe, including the hippocampus. "Our results do not necessarily mean that caffeine consumption hurts the brain," emphasizes Reichert. "But daily caffeine consumption affects our cognitive hardware, which in itself should give rise to further studies."

Cabozantinib for Metastatic Papillary Kidney Cancer

In a SWOG Cancer Research Network trial that put three targeted drugs to the test, the small molecule inhibitor cabozantinib was found most effective in treating patients with metastatic papillary kidney. The findings were published in *The Lancet*.

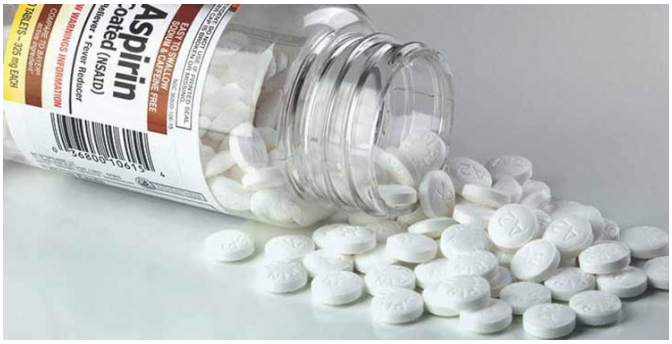
Sumanta Pal, MD, clinical professor of medical oncology at the City of Hope said there is hope for metastatic papillary kidney cancer patients. Mutations in the MET gene are a hallmark of this type of cancer, and there are new drugs that target the MET gene among other important signaling pathways. Pal decided to put three of them to the test against the current standard treatment, sunitinib, a receptor tyrosine inhibitor.

In his study, S1500, Pal studied 147 eligible patients with papillary kidney cancer, most of whom had not received any prior treatment. Patients were randomly assigned to one of four treatment groups—those who took sunitinib and those who took one of the three MET target drugs—cabozantinib, crizotinib, and savolitinib. Pal and his team wanted to see how long it would take patients' cancer to spread or return, a measure known as progression-free survival. It was found that patients receiving sunitinib went a median of 5.6 months before their cancer progressed; patients receiving savolitinib and crizotinib fared much worse overall. But cabozantinib, which inhibits VEGF receptors and AXL in addition to MET, gave patients a median of 9.2 months before their cancer progressed. Also, 23% of patients had a significant reduction in the size of their tumor with cabozantinib.

Aspirin Preferred to Prevent Blood Clots in Kids after Heart Surgery

Aspirin should be favoured over warfarin to prevent blood clotting in children who undergo surgery that replumbs their hearts, according to a new study. The research, led by the Murdoch Children's Research Institute (MCRI) and published in *The Journal of Thoracic and Cardiovascular Surgery*, will have implications for clinicians when prescribing blood-thinning medications after Fontan surgery, a complex congenital heart disease operation redirecting blood flow from the lower body to the lungs. MCRI Dr. Chantal Attard said although the operation couldn't completely 'fix' the heart, most were able to live well into adulthood and have relatively normal lives. But she said those who have the procedure were at an increased risk for blood clots.

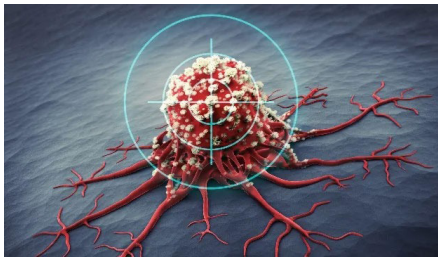
The study involved 121 patients enrolled in the Australian and New-Zealand Fontan (ANZ) Registry. It found stroke was common regardless of which medication the patient took. But patients on warfarin had poorer bone mineral density and were at a higher risk of bleeding. Dr. Attard said the research showed



for patients who undergo Fontan surgery, and do not have additional blood clotting risk factors; aspirin should be offered over warfarin. She said given the need for regular INR monitoring of warfarin, a shift to aspirin would also have a cost-benefit to the patient and the healthcare system. About 70,000 post-Fontan patients are alive today, with this number expected to double within two decades. She said the aspirin findings were a relief as the medication was much easier to manage and would benefit other families whose children required the procedure in the future.

Immunotherapy Target Identified for Brain Cancer

Scientists say they have discovered a potential new target for immunotherapy of malignant brain tumors. The discovery has been published in the journal *Cell*. Scientists from Dana-Farber Cancer Institute, Massachusetts General Hospital, and the Broad Institute of MIT and Harvard said the target they identified is a molecule that suppresses the cancer-fighting activity of immune T cells, the white blood cells that seek out and destroy virus-infected cells and tumor cells. The scientists said the molecule, called CD161, is an inhibitory receptor that they found on T cells isolated from fresh samples of brain tumors called diffuse gliomas. The CD161 receptor is activated by a molecule called CLEC2D on tumor cells and immune-suppressing cells in the brain, according to the researchers. Activation of CD161 weakens the T cell response against



tumor cells.

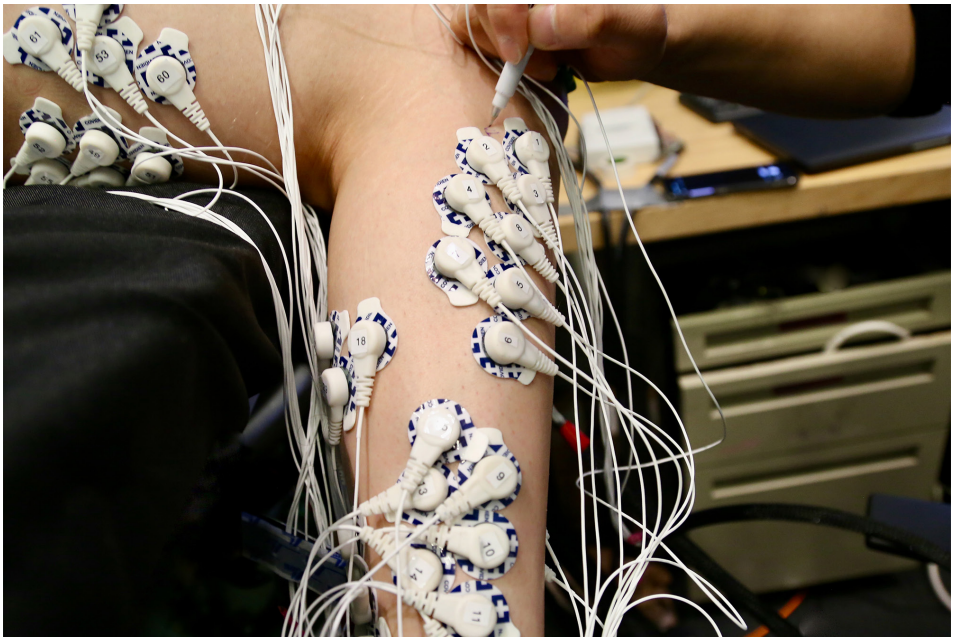
To determine if blocking the CD161 pathway could restore the T cells' ability to attack the glioma cells, the researchers disabled it in two ways: they knocked out the gene called KLRB1 that codes for CD161, and they used antibodies to block the CD161-CLEC2D pathway. In an animal model of gliomas, this strategy strongly enhanced the killing of tumor cells by T cells and improved the survival of the animals. The researchers were also encouraged because blocking the inhibitory pathway appeared to reduce T-cell exhaustion.

"We showed that this pathway is also relevant in several other major human cancer types," including melanoma, lung, colon, and liver cancer, said Kai Wucherpfennig, MD, Ph.D., director of the Centre for Cancer Immunotherapy Research at Dana-Farber. He is the corresponding author of the report along with Mario Suva, MD, Ph.D., of Massachusetts General Hospital; Aviv Regev, Ph.D., of the Broad Institute, and David Reardon, MD, clinical director of the Centre for Neuro-Oncology at Dana-Farber.

In the current study, the researchers found that fewer T cells from gliomas contained PD-1 than CD161. As a result, they said, "CD161 may represent a target, as it is a cell surface molecule expressed by both CD8 and CD4 T cell subsets and a larger fraction of T cells

express CD161 than the PD-1 protein." "Our comprehensive atlas of T cell expression programs across the major classes of diffuse gliomas thus identifies the CD161-CLEC2D pathway as a potential target for immunotherapy of diffuse gliomas and other human cancers," the authors of the report said.

Novel Surgery to Enable Better Control of Prosthetic Limbs



MIT researchers have invented a new type of amputation surgery that can help amputees to better control their residual muscles and sense where their "phantom limb" is in space. This restored sense of proprioception should translate to better control of prosthetic limbs, as well as a reduction of limb pain, the researchers say.

In a study in the *Proceedings of the National Academy of Sciences*, 15 patients who received agonist-antagonist myoneural interface (AMI) surgery could control their muscles more precisely than patients with traditional amputations. The AMI patients also reported feeling more freedom of movement and less pain in their affected limbs. "Through surgical and regenerative techniques that restore natural agonist-antagonist muscle movements, our study shows that persons with an AMI amputation experience a greater phantom joint range of motion, a reduced level of pain, and an increased fidelity of prosthetic limb controllability," says Hugh Herr, a professor of media arts and sciences, head of the Biomechatronics Group in the Media Lab, and the senior author of the paper.

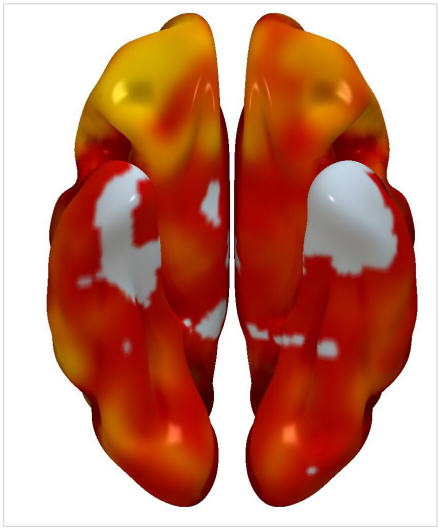
The researchers measured the precision of muscle movements in the ankle and subtalar joints of 15 patients who had AMI amputations performed below the knee. These patients had two sets of muscles reconnected during their amputation: the muscles that control the ankle and those that control the subtalar joint, which allows the sole to tilt inward or outward. The study compared these patients to seven people who had traditional amputations below the knee. Each patient was evaluated while lying down with their legs propped on a foam pillow, allowing their feet to extend into the air. Patients did not wear prosthetic limbs during the study. The researchers asked them to flex their ankle joints—both the intact one and the "phantom" one—by 25, 50, 75, or 100 percent of their full range of motion. Electrodes attached to each leg allowed the researchers to measure the activity of specific muscles as each movement was performed repeatedly. The researchers compared the electrical signals coming from the muscles in the amputated limb with those from the intact limb and found that for AMI patients, they were very similar. They also found that patients with the AMI amputation were able to control the muscles of their amputated limb much more precisely than the patients with traditional amputations.

"The AMI patients' ability to control these muscles was a lot more intuitive than those with typical amputations, which largely had to do with the way their brain was processing how the phantom limb was moving," said Srinivasan, a former member of the Biomechatronics group now working at MIT's Koch Institute for Integrative Cancer Research.

AMI patients reported much less pain and a greater sensation of freedom of movement in their amputated limbs. "They had a much greater sense of what their foot felt like and how it was moving in space," Srinivasan says.

Spanish Scientists Uncover Early Links between Cardiovascular Risk and Brain Metabolism

In a study carried out at the Centro Nacional de Investigaciones Cardiovasculares (CNIC) in partnership with Santander Bank and neuroimaging experts at the Barcelonaβeta Brain Research Center (BBRC, the research center of the Fundación Pasqual Maragall), the investigators have identified a link between brain metabolism, cardiovascular risk, and atherosclerosis during middle age, years before the first appearance of symptoms. The report, published in the *Journal of the American College of Cardiology (JACC)* suggests that intervention in a modifiable condition (cardiovascular disease) could prevent the development of dementia.



The CNIC-coordinated study, led by Dr. Marta Cortés Canteli, shows that in middle age, years before any clinical signs appear, atherosclerosis and cardiovascular risk factors already show an association with low metabolism in brain regions implicated in the future development of dementia, especially Alzheimer's disease. Using advanced imaging by positron emission tomography (PET), the research team quantified brain metabolism in more than 500 participants in the PESA-CNIC-Santander study. The participants had an average age of 50 years and no symptoms, but already had evidence of atherosclerosis in their arteries.

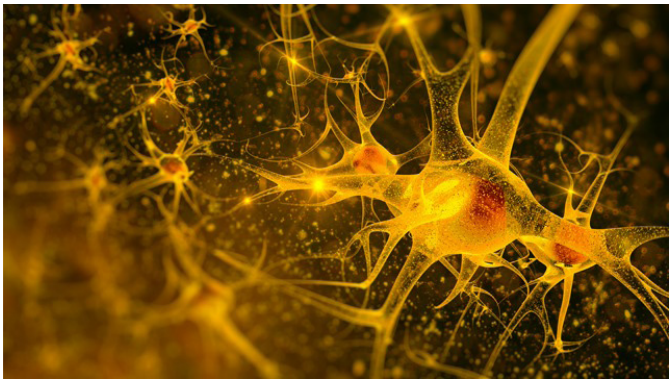
The new study reveals a link between the elevated risk of a cardiovascular event and low brain metabolism. "When brain metabolism declines, the brain's ability to handle adverse events can be compromised. Depending on the brain area affected, this can lead to a range of distinct problems," explained study co-first author Dr. Cortés Canteli, a CNIC investigator, and Miguel Servet fellow.

"We found that a higher cardiovascular risk in apparently healthy middle-aged individuals was associated with lower brain metabolism in parietotemporal regions involved in spatial and semantic memory and various types of learning," said Dr. Cortés Canteli. Dr. Juan Domingo Gispert, head of the Neuroimaging group at the BBRC, noted that "the brain areas showing low metabolism in participants with higher cardiovascular risk are the same areas affected in Alzheimer's disease, suggesting that these individuals may have higher than normal vulnerability to this disease."

The research team also found that a higher number of plaques in the carotid arteries, which carry blood to the brain, was associated with lower brain metabolism in areas of the limbic system and the parietal lobe, both of which are intimately linked to the development of Alzheimer's disease.

Lack of Oxygen Makes Nerve Cells Grow

Scientists from the University Hospitals of Copenhagen and Hamburg-Eppendorf, researchers from the Max Planck Institute for Experimental Medicine in Göttingen have shown in mice that mentally and physically demanding activity triggers not only a local but also a brain-wide "functional hypoxia." The shortage of oxygen activates the growth factor erythropoietin (EPO), which stimulates the formation of new synapses and nerve cells.



In a new study, the research group examined in detail which brain regions and cell types are affected by the shortage of oxygen. They used genetically modified mice that produce a molecule throughout the brain that leads to the formation of a fluorescent dye when there is an oxygen deficit. To challenge the mice

both mentally and physically, the researchers let them run on specially prepared running wheels for several days. Mice that had no access to a running wheel and mice exposed to oxygen-depleted air served as comparator groups. The researchers also examined the activation of genes in different brain regions and cell populations to find out how the brain reacts to activity-induced hypoxia.

In both cases, the change in the activity of many genes was similar, and a mild oxygen deficit occurred throughout the brain. However, there were major differences between different cell types: nerve cells were particularly affected, whereas the glial cells (auxiliary cells of the neurons) were only slightly affected. Also, the EPO gene in the brain, together with several other genes, is particularly stimulated during both mental and physical activity. "We still don't know whether mild hypoxia as a result of activity also leads to stronger networking of nerve cells in humans. We, therefore, want to carry out similar studies on humans—for example on test subjects who are active on exercise bikes," says Hannelore Ehrenreich, head of the study. The findings could ultimately benefit patients with neurodegenerative diseases in which nerve cells die or lose synapses.

Geisinger Researchers Find AI Can Predict Death Risk

Researchers at Geisinger have found that a computer algorithm developed using echocardiogram videos of the heart can predict mortality within a year. The algorithm outperformed other clinically used predictors, including pooled cohort equations and the Seattle Heart Failure score. The results of the study were published in *Nature Biomedical Engineering.*

"We were excited to find that machine learning can leverage unstructured datasets such as medical images and videos to improve on a wide range of clinical predic-

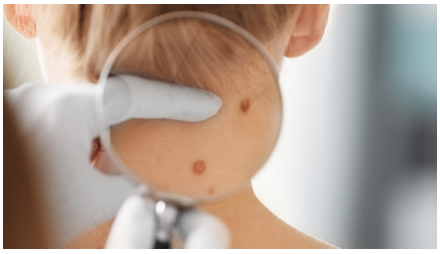
tion models," said Chris Haggerty, Ph.D., co-senior author, and assistant professor in the Department of Translational Data Science and Informatics at Geisinger. Imaging is critical to treatment decisions in most medical specialties and has become one of the most data-rich components of the electronic health record (EHR). For their study, the research team used specialized computational hardware to train the machine learning model on 812,278 echocardiogram videos collected from 34,362 Geisinger patients over the last ten years. The study compared the results of the model to cardiologists' predictions based on multiple surveys. A subsequent survey showed that when assisted by the model, cardiologists' prediction accuracy improved by 13 percent.

New Treatment Extends Life of Advanced Melanoma Patients

A new study has revealed that drug treatment before surgery is effective in preventing melanoma. The study, published in *Nature Medicine*, pooled data from six clinical trials where drug therapy was given before surgery, known as neoadjuvant therapy.

Researchers found that giving Stage III patients a short course of pre-operative targeted immunotherapy was effective, and the stronger a patient's response to that treatment in the first six to nine weeks, the greater the likelihood their disease would not recur after surgery. In 75% of patients who responded well to dual immunotherapy given before surgery, only 3% saw their tumors return after surgery, suggesting that 97% will likely be cured. "The neoadjuvant approach is a new way of dealing with melanoma and is a game-changer for stage III patients with bulky disease that has spread to their lymph nodes," said Professor Georgina Long AO, Melanoma Institute Australia (MIA) Co-Medical Director and study senior author.

Data from the study suggests



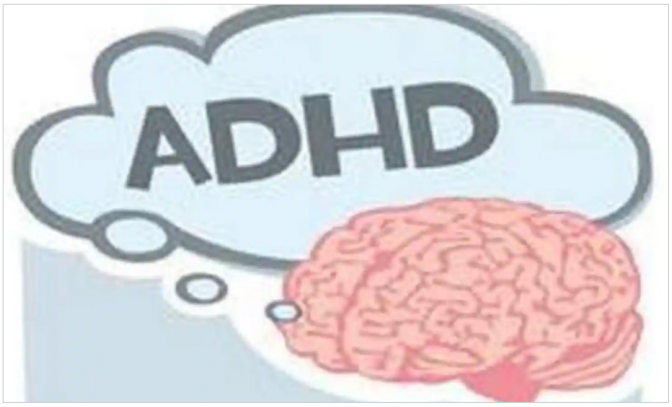
that immunotherapy may work more effectively when given before, rather than after surgery, due to the presence of the bulky tumor provoking an immune response. In addition to training the immune system to work more effectively against melanoma, neoadjuvant

therapy also enables a clinician to assess early on if a patient is responding to a particular treatment and decide on an alternative plan if needed. It can also make surgery less complex.

Associate Professor Alex Menzies, MIA Oncologist and study the first author, said; "This study shows that giving drug therapy before surgery reduces the risk of recurrence even further, preventing spread to vital organs like the brain and liver and saving more lives.

Brain Connectivity Can Serve As a Machine Learning Biomarker for Attention ADHD

A new study has discovered how brain connectivity can be used as a biomarker for Attention Deficit Hyperactivity Disorder (ADHD). The research published in the journal *'Frontiers in Physiology'* relied on machine-learning classifiers to identify with 99 percent accuracy the adults who had received a childhood diagnosis of ADHD many years earlier.



"This suggests that brain connectivity is a stable biomarker for ADHD, at least into childhood, even when an individual's behavior had become more typical, perhaps by adapting different strategies that obscure the underlying disorder," said Chris McNorgan, an assistant professor of psychology in the UB College of Arts and Sciences, and the study's lead author. The findings have implications for not only detecting ADHD but can also help clinicians target treatments by understanding where patients sit on a broad-spanning continuum.

The multidisciplinary research team of UB undergraduate research volunteers Cary Judson from the Department of Psychology and Dakota Handzlik in the Department of Computer Science and Engineering, and John G. Holden, an associate professor of psychology at the University of Cincinnati, used archival fMRI data from 80 adult participants who were diagnosed with ADHD as children. Machine learning classifiers were then applied to four snapshots of activity during a task designed to test the subject's ability to inhibit an automatic response. Focused analysis of individual runs achieved 91 percent diagnostic accuracy, while the collective analysis came close to 99 percent.