Using fruit flies to unlock mysteries of human diabetes

By Krista Conger

For the first time, the tiny fruit fly can be used to study how mutations associated with the development of diabetes affect the production and secretion of the vital hormone insulin.

The advance is due to a new technique devised at the School of Medicine that allows scientists to measure insulin levels in the insects with extremely high sensitivity and reproducibility.

The experimental model is likely to transform the field of diabetes research by bringing the staggering power of fruit fly genetics, honed over 100 years of research, to bear on the devastating condition.

The experimental model is likely to transform the field of diabetes research by bringing the staggering power of fruit fly genetics, honed over 100 years of research, to bear on the devastating condition.

Suicide risk increases in sleepless older adults

By Becky Bach

Older adults suffering from sleep disturbances are more likely to die by suicide than well-rested adults, according to a study led by a researcher at the School of Medicine.

“Suicide is one of the least stigmatized of suicides, and it is among the least likely to be considered a mental health issue,” said Rebecca Bernert, PhD, lead author of the study. Bernert is an instructor of psychiatry and behavioral sciences and director of the Suicide Prevention Research Laboratory at Stanford.

The study was published Aug. 13 in JAMA Psychiatry. Bernert said older adults have disproportionately higher rates of suicide risk compared to

As children memorize facts, brains reorganize

By Erin Digitale

As children learn basic arithmetic, they gradually switch from solving problems by counting on their fingers to pulling facts from memory. The shift comes more easily for some kids than for others, but no one knows why.

Now, new brain-imaging research gives the first evidence drawn from a longitudinal study to explain how the brain reorganizes itself as children learn math facts. A precisely orchestrated group reorganizes itself as children learn math facts.

The results, which were published online Aug. 17 in Nature Neuroscience, explain brain reorganization during normal development of cognitive skills and will serve as a point of comparison for future studies of what goes awry in the brains of children with learning disabilities.

“We wanted to understand how children acquire new knowledge, and determine why some children learn to retrieve facts from memory better than others,” said Vinod Menon, PhD, the Rachael L. and Walter F. Nichols, MD, Professor of psychiatry and behavioral sciences, who is the senior author of the study. "This work provides insight into the dynamic changes that occur over the course of cognitive development in each child.

The study also adds to prior research into the differences between how children's and adults' brains solve math problems. Children use certain brain regions, including the hippocampus and the prefrontal cortex, very differently from adults when the two groups are solving the same types of math problems, the study showed.

It was surprising to us that the hippocampal and prefrontal contributions to memory-based problem-solving during childhood don't look anything like what we would have expected for the adult brain,” said postdoctoral scholar Shaosheng Qin, PhD, who is the paper's lead author.

Charting the shifting strategy

In the study, 28 children solved simple math problems while receiving two functional magnetic resonance imaging brain scans; the scans were done about 1.2 years apart. The researchers also scanned 20 adolescents and 20 adults at a single time point. At the start of the study, the children were ages 7-9. The adolescents were 14-17, and the adults were 19-22. The participants had normal IQs. Because the study examined normal math learning, potential participants with math-related learning disabilities and attention deficit

Heart drug tied to increased risk of death in patients with atrial fibrillation

By Becky Bach

In An Account of the Foxglove and Some of its Medical Uses, published in 1785, Sir William Withering cautioned readers that foxglove was not a perfect drug. “Time will fix the real value upon this discovery,” he wrote.

Foxglove, a genus of flowering plants, contains cardiac glycosides, which can be used to treat heart failure and atrial fibrillation — a rapid and irregular heart rhythm. Now, more than 200 years later, researchers at the School of Medicine have validated Withering’s warning with the discovery that patients with atrial fibrillation who are treated with digoxin, a glycoside commonly extracted from woolly foxglove, are more likely to die than similar patients who received different treatments.

“The take-home point is to question whether people should really be on this drug,” said the study’s lead author, Mintu Turakhia, MD, assistant professor of cardiology at Stamford and director of cardiac electrophysiology at the Veterans Affairs Palo Alto Health Care System. “These data challenge the use of digoxin, which is an outdated drug. “Time will fix the real value upon this discovery,” said Sir William Withering, published in 1785, Sir William Withering cautioned readers that foxglove was not a perfect drug. “Time will fix the real value upon this discovery.”
Low oxytocin levels not linked to all cases of autism, study finds

By Erin Digita1

Autism does not appear to be solely caused by a deficiency of oxytocin, but the hormone’s universal ability to boost social function may prove useful in treating a subset of children with the developmental disorder, according to new findings from the School of Medicine and Lucile Packard Children’s Hospital Stanford.

Low levels of oxytocin, a hormone involved in social functioning, have for years been suspected of causing autism. Prior research seeking a link has produced mixed results. Now, in the largest-ever study to test the purported connection, the range of blood oxytocin levels has been shown to be the same in children with autism as that observed in two comparison groups: children with autistic siblings and children without autistic siblings. In other words, similar numbers of children with low, medium and high oxytocin levels were found in all three groups.

A paper describing the new findings was published online Aug. 4 in Proceedings of the National Academy of Sciences.

Although autism was not directly linked to oxytocin deficiency, the Stanford team found that higher oxytocin levels were linked to better social functioning in all groups. All children with autism have social deficits, but in the study these deficits were worse in those with the lowest blood oxytocin and mildest in those with the highest oxytocin. In the comparison groups, children’s social skills also fell across a range that correlated to their oxytocin levels.

Regulator of social functioning

“Oxytocin appears to be a universal regulator of social functioning in humans,” said Karen Parker, PhD, assistant professor of psychiatry and behavioral sciences and the lead author of the study. “That encompasses both typically developing children as well as those with the severe social deficits we see in children with autism.”

Autism is a developmental disorder that affects 1 of every 68 children in the United States. It is characterized by social and communication deficits, repetitive behaviors and sensory problems. The new study included 79 children with autism, 52 of their unaffected siblings and 62 unrelated children without autism. All of the children were between the ages of 3 and 12.

“It didn’t matter if you were a typically developing child, a sibling or an individual with autism: Your social ability was related to a certain extent to your oxytocin levels, which is different from what people have speculated,” said Antonio Hardan, MD, professor of psychiatry and behavioral sciences and the study’s senior author. Hardan is a child and adolescent psychiatrist who treats children with autism at the hospital.

In previous hypotheses saying that low oxytocin was linked to autism were maybe a little bit simplistic,” he said. “It’s much more complex: Oxytocin is a vulnerability factor that has to be accounted for, but it’s not the only thing leading to the development of autism.”

The researchers caution, however, that blood oxytocin measurements may be different than oxytocin levels in the cerebrospinal fluid bathing the brain, which they did not measure.

In addition to examining oxytocin levels, the researchers examined the importance of small variations in the gene coding for the oxytocin receptor. Certain receptor variants were correlated to higher scores on standard tests of social ability, the study found.

The team also discovered that blood levels of oxytocin are highly variable: The levels are influenced by inheritance to about the same degree as adult height, which is often described as being strongly influenced by genetics.

Inheriting social abilities

What our study hints at is that social behavior may be heritable in families,” Parker said. “That will help guide future research to determine whether oxytocin is a useful autism treatment. The new findings suggest that some children with autism — such as the subset of kids with autism who have naturally low oxytocin levels, or those with oxytocin receptor genes associated with worse social functioning — might benefit most from oxytocin-like drugs.

“Autism is so heterogeneous,” Parker said. “If we can identify biomarkers that help us identify the patients most likely to benefit from a specific therapy, we expect that will be very useful.”

Other Stanford co-authors of the study are Joseph Garner, PhD, associate professor of comparative medicine; Robin Libove, social science research assistant; Shelly Hyde, laboratory manager; Kirsten Hooten, medical student; Dean Carson, PhD, postdoctoral scholar; Chun-Ping Liao, life science research assistant; Jennifer Phillips, PhD, clinical associate professor of psychiatry and behavioral sciences and co-director of the Autism and Developmental Disabilities Clinic at Lucile Packard Children’s Hospital Stanford; and Joachim Hallmayer, associate professor of psychiatry and behavioral sciences.

Parker, Hardan, Garner and Hallmayer are members of Stanford’s Child Health Research Institute.

The research was supported by grants from the Simons Foundation Autism Research Initiative, the Mosbacher Family Fund for Autism Research, the Escher Fund at the Silicon Valley Community Foundation, Stanford’s Child Health Research Institute and the National Institutes of Health.

Stanford’s Department of Psychiatry and Behavioral Sciences also supported the work. Information about ongoing Stanford research in oxytocin therapy for children with autism is available at http://med.stanford.edu/clinicaltrials/trials/NCT01624194. More information about related research can be found at https://web.stanford.edu/group/autism.

Scientists create remote-controlled nanoscale protein motors

By Shara Tonn

In every cell in your body, tiny protein motors are toiling away to keep you moving. Gobbling, dividing cells, twisting DNA — they are the workhorses of biology. But there is still uncertainty about how they function. To help biologists in the quest to know more, a team of Stanford bioengineers has designed a suite of protein motors that can be controlled remotely by light.

“Biology is full of these nanoscale machines that can perform complex tasks,” said Zev Bryant, PhD, assistant professor of bioengineering. “We want to understand how they can convert chemical energy into mechanical work and perform their specific tasks in cells.”

Bryant’s team, including doctoral student Muneaki Nakamura, designed blueprints for protein motors that would respond to light. Splicing together DNA from different organisms such as pig, slime mold and oat — the oat had the light-detecting module — the bioengineers created DNA codes for each of their protein motors.

The remote-controlled nanomotors are described in a paper that appeared online Aug. 3 in Nature Nanotechnology. Bryant is senior author of the paper, and Nakamura is the lead author.

When exposed to light, the new protein motors change direction or speed.

“It’s pretty fine spatial control; you can decide where the light is and where it isn’t, and control motors in this very exquisite way,” Bryant said. Being able to control the motors in real time should be a boon for cell and developmental biologists trying to study forces and motion in living things.

“It’s an entirely new project for us to be moving inside cells and organisms and to be working more closely with biologists,” Bryant said. Now that he and his team have a basic blueprint, they will be able to customize these motors for biologists who are looking into specific tasks.

“Before we can fully play with our system, I hope that we can provide cell biologists with tools that allow them to change very dramatically the viewpoints of molecular motors in their cellular contexts,” Bryant said.

Bryant’s lab also has the possibility of using the controllable motors outside of biology, in diagnostic devices, for example. Bryant noted that researchers have worked on harnessing molecular motors to perform functions similar to their biological roles, “transporting molecules, sorting molecules, and concentrating molecules.”

But first and foremost, Bryant is rebuilding these motors — incorporating them into devices for the biofuel industry and in an effort to illuminate their true nature.

“Evolution takes a basic design and makes motors that are fast and motors that are slow and motors that move long distances,” Bryant said. “We’ve tried to build diverse motors and really challenge our understanding by pushing boundaries of what’s possible outside of what’s already been done by evolution.”

Other Stanford co-authors of the paper are graduate students Lu Chen and Tony Schindler. Researchers of UC-Berkeley also contributed to the study.

The work was supported by a Sloan Award, the National Institutes of Health, an American Heart Association predoctoral fellowship, and Stanford’s Science Foundation Graduate Research Fellowship, a Stanford Graduate Fellowship and Howard Hughes Medical Institute.
Cancer-causing mechanism behind oncogene uncovered

By Krista Conger

A protein present at high levels in more than half of all human cancers drives cell growth by blocking the expression of just a handful of genes involved in DNA packaging and cell death, according to a new study by researchers at the School of Medicine.

The researchers found that the protein, called Myc, works through a tiny regulatory molecule called a microRNA to suppress the genes’ expression. It marks the first time that a subset of Myc-dependent cancer cells identified as critical players in the protein’s cancer-causing function, and suggests new therapeutic targets for Myc-dependent cancers.

“This is a different way of thinking about the roles of microRNA and chromatin packaging in cancer,” said Dean Felsher, MD, PhD, professor of oncology and of pathology. “We were very surprised to learn that the overexpression of one microRNA can mimic the cancerous effect of Myc.”

Felsher is the senior author of the study, which was published Aug. 11 in Cancer Cell. The lead author is instructor Yulin Li, MD, PhD.

The genes identified by the researchers revealed that genes that govern whether a cell self-renews by dividing, enters a resting state called senescence or takes itself permanently out of commission through programmed cell suicide. Exquisitely control of these processes is necessary to control or eliminate potentially dangerous tumor cells.

The gene encoding the Myc protein is a well-known and potent oncogene—a term used to describe genes that cause cancer when mutated or abnormally expressed. It regulates the expression of around 10,000 genes and microRNAs in a cell.

Scientists have long known that inactivating Myc, or blocking its expression, can cause Myc-dependent cancer cells to stop growing or die, as well as cause tumor regression in mice with Myc-dependent solid cancers. This type of dependence is called oncogene addiction. MicroRNAs are small RNA molecules (only about 22 nucleotides long) that can, like Myc, regulate gene expression.

Previous research had shown that Myc overexpression can increase the number of sites within a family of microRNAs called miR-17-92.

“Myc provides new insights into the tumor-suppressive mechanisms of just a handful of genes involved in DNA packaging,” said Felsher. “But it wasn’t clear how this was related to Myc’s oncogenic function.”

Li found that Myc-dependent cancer cells — either grown in a laboratory dish or implanted as a tumor in mice — in which miR-17-92 expression was blocked. This suggested that a subset of genes worked through the microRNA family to exert its cancer-causing effects.

Li then looked for an overlap among genes affected by Myc overexpression and those affected by miR-17-92. Of these, the team found about 401 genes whose expression was either increased or suppressed by both Myc and miR-17-92. They chose to focus on genes that were suppressed because these genes exhibited on average many more binding sites for the microRNAs. They further winnowed their panel to 15 genes regulated by more than one miR-17-92 binding site.

Of these, five stood out. Four encode proteins known to regulate how DNA is tightly packaged around proteins (creating a complex called chromatin). This packaging is necessary to allow the DNA to fit within a cell’s nucleus, but it makes it difficult for proteins regulating transcription to access genes. The four proteins controlled by Myc and miR-17-92 affect cell proliferation and senescence by regulating gene accessibility within the chromatin. They had never before been identified as Myc or miR-17-92 targets.

To further explore this idea, the researchers introduced a protein called Bim that induces programmed cell death, or apoptosis. This cellular suicide pathway is failing in the body to eliminate damaged or unneeded cells. Bim expression had been previously reported to be affected by miR-17-92.

Notably, all of the proteins are known to affect either cellular proliferation, entry into a resting state of the cell cycle or apoptosis, in part by granting or blocking access to genes in tightly packed stretches of DNA in the chromatin.

“Myc is a general amplifier of gene transcription and expression,” said Felsher, “but our study shows that the maintenance of the cancerous state relies on more-focused mechanisms.”

Finally, Li and his colleagues showed that suppressing the expression of the five target genes, effectively mimicking Myc overexpression, partially mitigates the effect of Myc deactivation.

Up to 30 percent of Myc-dependent cancer cells in culture continued to grow (in contrast to only 11 percent of control cells) in the absence of Myc expression, and tumors in mice either failed to regress or recurred within a few weeks.

“One of the biggest unanswered questions in oncology is how oncogenes cause cancer, and whether you can replace an oncogene with another gene product,” said Felsher. “These experiments begin to reveal how Myc affects the self-renewal decisions of cells. They may also help us target those aspects of Myc overexpression that contribute to the cancer phenotype.”

Other Stanford co-authors of the paper are former postdoctoral scholar Peter Choi, PhD, postdoctoral scholar Stephane Casey, PhD, and professor of computer science David E. Pichler.

The research was supported by the National Institutes of Health, the Leukemia and Lymphoma Society and the King Abdullah University of Science and Technology.

Stanford’s Department of Medicine and Department of Pathology also supported the work.

The Perfect 46 examines ethical dilemmas of genetic screening

By Becky Bach

The company’s promise is simple, and alluring. Send it your DNA and your genome, along with your partner’s, and its proprietary algorithm will determine whether your children will be born free of genetic defects—or not.

“Jesse [Darden, the company’s CEO] wasn’t going to cure the diseases; he would just breed them out. It made a lot of people comfortable,” says company senior vice president Ronald Khan, played by actor Sheldon Coolman, in The Perfect 46, a movie about the dilemmas of genetic screening and matchmaking.

Written and directed by Brett Ryan Bonowicz, the feature-length film traces Darden’s personal and professional history with a few fellow geneticists, a bioethicist and the filmmaker. The fifth-encodes a protein called Bim that induces programmed cell death, or apoptosis. This cellular suicide pathway is failing in the body to eliminate damaged or unneeded cells. Bim expression had been previously reported to be affected by miR-17-92.

“Technologically, it’s very hard to do,” Hill said.

In addition, scientists don’t know what every version of a particular gene does.

“Often, we don’t know if it’s disease-causing or not,” said panelist Michael Snyder, PhD, Stanford professor and chair of genetics.

Snyder said he sequenced his own genome — and by his own account — and discovered a genetic predisposition for type-2 diabetes, a condition he soon developed.

“The fourth,” he said, “is something he can’t interpret, he may find something unexpected or he may even find something that dis-
Six or so years ago, Frank Longo, MD, PhD, Stanford's chair of biochemistry and biological sciences, was optimistic that a treatment for Alzheimer's disease was on its way. More than a decade earlier, pharmaceutical companies had begun testing drugs to eradicate one of its hallmark signs — clumps of protein sprinkled randomly throughout the brain. The drugs were antibodies that bind to the protein, called beta amyloid, or A-beta for short. “They poured a lot of money into clinical trials of these antibodies in Alzheimer's patients,” Longo said. “And by around five years ago with the conclusion of early-stage trials, it looked like they might succeed. So, many in the field — including me — had some guarded optimism that when the pivotal phase-3 trials were completed, this approach would have at least some beneficial effect.” On the order of 30 million people worldwide, including more than 5 million Americans, have Alzheimer's, the most common form of dementia, which raids the brain and steals a person's ability to remember, reason and imagine. Barring substantial progress in curing or preventing it, Alzheimer's will affect 16 million U.S. residents by 2050, according to the Alzheimer's Association. The group also reports that the disease is now the nation's most expensive, costing over $200 billion a year. Recent analyses suggest it may be as great a killer as cancer or heart disease. It's not really clear what causes the disease, and even rendering a diagnosis involves some guesswork. Genetic factors have been shown to contribute to the likelihood of getting it, but none among them comes close to fully predicting or explaining its onset and progression. What's known is that the diseased brain is characterized by the protein clumps outside of nerve cells and tangles of fibrous filaments within them, accompanied by an accelerating die-off of nerve cells. And that there is no cure. So it was unfortunate that three separate phase-3 trials testing the antibody strategy all failed to have any therapeutic effect on cognition. “I'd like to have baro systems better to offer my patients,” said Longo, who directs the Stanford Center for Memory Disorders. “It's profoundly disappointing when that doesn't happen. In the wake of this disappointment, research to understand Alzheimer's has shifted focus. Instead of trying to address signs and symptoms seen in the end-stage disease, researchers are looking at what goes wrong much earlier. Their insights have yielded promising new imaging techniques and new targets for therapeutic drugs, with at least a couple of promising startup companies Stanford researchers have spun off. When the brain's brakes lock up “By the time visible symptoms of dementia appear and a patient first sees a doctor about it, this process has been under way for years,” said Carla Shatz, PhD, a professor of physiology and biology and the director of Neurosciences, the brain's own set of immune cells, called microglia, which can secrete C1q. Other cells called astrocytes secrete the rest of C1q's complement-system "reagents." The two cell types work analogously to the two tubes of an epoxy kit, in which one tube contains the resin, the other a catalyst. “This relentless fidgeting is the physiological basis of learning, ramifying and daydreaming; a fire burning through the brain “In our early development, our brains sprout a surplus of synaptic connections. This redundancy allows for myriad potential brain circuits, but as we begin life within the bounds of our genes and environmental interaction, we prune away the excess synapses through a process called "pruning" of redundant or counterproductive connections. An excess of extraneous synaptic connections means that the brain is maintaining a suboptimal stage of cognitive efficiency from raw marble, the brain has tools, including the complement system, for pruning unused or unfunctional synapses through a process called complement cascade activity. Barring this the brain's immune response to the experience and development, synapses are in a throbbing state of flux: being born, enlarging and strengthening, diminishing and weakening, or disappearing altogether. This relentless fidgeting is the physiological basis of learning, ramifying and daydreaming; A fire burning through the brain In our early development, our brains sprout a surplus of synaptic connections. This redundancy allows for myriad potential brain circuits, but as we begin life within the bounds of our genes and environmental interaction, we prune away the excess synapses through a process called "pruning" of redundant or counterproductive connections. An excess of extraneous synaptic connections means that the brain is maintaining a suboptimal stage of cognitive efficiency from raw marble, the brain has tools, including the complement system, for pruning unused or unfunctional synapses through a process called complement cascade activity. Barring this the brain's immune response to the experience and development, synapses are in a throbbing state of flux: being born, enlarging and strengthening, diminishing and weakening, or disappearing altogether. This relentless fidgeting is the physiological basis of learning, ramifying and daydreaming;
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Researchers are seeking healthy children aged 4 to 8 to volunteer for a study of how the brain responds to the taste of chocolate milkshakes.

By Erin Digitale

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By Erin Digitale

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Diabetes
continued from page 1
Sangbin Park, PhD, is the lead author of the paper, published Aug. 7, in PLOS Genetics.
Developed by Park, the new technique uses a chemical tag to label an insulin-like peptide called Ilp2 in fruit flies. The tag allows researchers to use an antibody-assisted assay to measure insulin concentrations in the insects’ blood and cells at the picomolar level—the level at which insulin concentrations are measured in mice.
“I normally avoid the term, but I think Dr. Park’s new technique is a true breakthrough,” said Howard Hughes Medical Institute investigator. “Only in selected mammals can researchers measure insulin with this degree of sensitivity.”

The power of a tiny model system
Insulin is an ancient molecule used by nearly all animals to regulate metabolism, growth and development. Diabetes in humans occurs when insulin-producing cells in the pancreas fail to produce enough insulin or when the body’s cells grow resistant to its effects. In 2002, Kim, his lab team and fellow Stanford researchers discovered that fruit flies develop a diabetes-like condition when their insulin-producing cells are destroyed.

Teenagers are not the only ones to suffer from diabetes in fruit flies. The scientists also saw changes in the brain’s activity patterns when a fly carries a mutation in the Ilp2 protein. “The Ilp2 protein is lethal. Then random inserted chemical tags along the length of the molecule to create a panel of molecules tagged in many different places. Testing them individually, he learned which parts of the flies — indicating that the molecule’s activity had not been compromised. Eventually he found two locations on Ilp2 that were ideal. He could then use antibodies that recognized the tags to quantify levels of Ilp2 with the antibody-based assay.

“Once you know that the modifications, or tags, don’t affect the expression of the protein, you have a lot more power to interpret your experiments,” said Kim. “You can begin to use the insula assembly line, from the transcription of RNA from the gene, to the production of the protein, to the storage and eventual release of the protein in response to metabolic signals. You have the opportunity to figure out the mechanisms controlling each of these steps in detail.”

In flies, Ilp2 is produced and secreted by specialized neurons in the brain. This results in relatively high levels of circulating Ilp2 with the amount of mature but unsecreted Ilp2: simply converting the amount of Ilp2 into the amount in their brains.

Park found that the amount of secreted Ilp2 increased from about 0.1 percent to about 0.35 percent of the total available during the first three days of a fruit fly’s life. Furthermore, like in humans, circulating Ilp2 concentrations were relatively low in fasting flies, but peaked and then declined after a subsequent meal. Finally he showed that, in flies with only one working copy of the insulin receptor gene (they normally have two), as do human children with the insulin secretion was in an apparently attempt to compensate for the deficiency — mirroring the development of insulin resistance in human children’s brains.

Park and his colleagues then turned their attention to mutations associated with type-2 diabetes. “The research was funded by the How-
ard Hughes Medical Institute, Stanford’s Department of Psychiatry and Behavioral Sciences also supported the work. iSM

Math
continued from page 1
hyperactivity disorder were excluded. The children and adolescents who took part in the research did not provide any math instruction.

During the study, as the children aged from an average of about 7 to 9.4 years, they were able to respond more accurately at solving math problems, and relied more on retrieving math facts from memory and less on counting. As these shifts in strategy took place, the researchers saw several changes in the children’s brains. The hippocampus, a region with many roles in shaping new memories, was activated more in children’s brains after one year. Regions involved in counting, including parts of the prefrontal and parietal cortex, were activated less.

The scientists also saw changes in the degree to which the hippocampus was connected with other parts of the brain. In children with math problems, the hippocampus was still connected with several parts of the prefrontal, anterior temporal cortex and parietal cortex more strongly connected to the brain’s motor and sensory areas. “As these connections, the greater was each individual child’s ability to retrieve math facts from memory, a finding that suggests a starting point for future studies of math learning capabilities,” said Menon.

Although children were using their hippocampus more after a year, adolescents and adults made minimal use of the hippocampus when solving math problems. Instead, they pulled math facts from well-developed in-memory representations, said Menon.

Memory scaffold
“With this means that the hippocampus is providing good representations of math facts in other parts of the brain as adultlike neural connections for solving math problems are being constructed. In adults this scaffold is not needed because memory for math facts has most likely been consolidated into the neocortex,” he said.

Interestingly, the research also showed that, although the children and adolescents had not yet reached the adult stage of memory consolidation in their hippocampus, they are still able to take advantage of its ability to form new memories. “The hippocampus activity: “Blood, sweat and fears,” a first-person account of the disease investigation in mice and humans.”

The next step, Menon said, is to compare the new findings about normal math learning to changes in children with math learning disabilities.

“With children in math-learning disabilities, we’re trying to retrieve things that influenza is a basic problem, and remains a bottleneck for them in high school and college,” he said. “Is that the scaffold to build good representations of math facts in other parts of the brain during the early stages of learning, and so the child continues to use inefficient strategies to solve math problems?” We want to test this.”

Other Stanford co-authors of the study are former postdoctoral scholar Sodhyon Cho, PhD; postdoctoral investigators Tianhui Jiang and Minah Mirambeinsfard; and Miriam Roley, Lee, PhD, instructor in psychiatry and behavioral sciences.

The research was supported by the National Institute of Health, Stanford’s Child Health Research Institute, the Lucile Packard Foundation for Children’s Health, the National Science Foundation’s Graduate Research Award and the Netherlands Organization for Scientific Research.

Stanford’s Department of Psychiatry and Behavioral Sciences also supported the work. See MAGAZINE, page 7

The medical school’s Office of Communications & Public Affairs recently earned national honors for the magazine it produces and for its blog.

The spring 2013 issue of Stanford Medicine magazine, which included a feature package of stories about blood, sweat and fears, received a gold award in the education category from the Council for the Advancement and Support of Education, known as CASE.

The judges for the category noted that “we expected publications to present a single topic from multiple perspectives, which Stanford Medicine accomplished with great variety and depth. There was great variety and depth of content around the central subject matter, coupled with leads that pulled the reader right into each story, making the magazine both superior writing and creative angles for each story.”

The judges went on to say that two themes dominated the story package: “excellent writing and vivid imagery; the covers were fantastic.”

Gold award for gold writing
Additionally, the magazine received its third consecutive CASE gold award in the periodical staff writing category. The collection of five stories in the entry featured Grace Kim and Sydne Tomes.

“Blood, quest,” which describes Stanford’s historic role in developing the cure for sickle cell anemia, merited the gold award. “Tip of the iceberg,” a feature on a poten-

Medical school magazine, blog earn awards
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Suicide

other age groups, making suicide prevention in elderly populations a pressing public health challenge.

Using data from an epidemiological study of 14,456 adults aged 65 and older, Bernert and her colleagues compared the sleep quality and potential treatment target of 20 who died by suicide with the sleep patterns of 400 similar individuals from a 10-year period. They found that participants reporting poor sleep had a 1.4 times greater chance of death by suicide within a 10-year period than participants who reported sleeping well.

The study confirmed the relationship between depression and suicide risk, while also assessing poor sleep patterns of 400 similar individuals from a 10-year period. Bernert said. “Disturbed sleep stands apart as a risk factor and potential treatment target in suicide prevention.”

“Suicide is preventable,” she added. “Interventions for suicide prevention are alarmingly scarce.”

Bernert has two studies now underway testing the effectiveness of an insomnia treatment for the prevention of depression and suicidal behaviors.

Most of the study’s suicide decedents were white men, a group at heightened risk for suicide in the general population, Bernert said, noting that additional research is needed to see if the correlation between disturbed sleep and suicide risk extends to women, minorities and younger adults or teenagers.

Bernert recommended organizations such as the American Foundation for Suicide Prevention (http://www.afsp.org) and the National Suicide Prevention Lifeline (1-800-273-TALK) as resources for people who are struggling with thoughts of suicide.

Other co-authors of the study are affiliated with the VA-Palo Alto, University of Pennsylvania, the Veterans Affairs Eastern Colorado Health Care System and the University of Colorado-Denver also contributed to the study.

This study was funded by a Veterans Health Services Research and Development Career Development Award, an American Heart Association National Scientist Development grant, a VA Health Services and Development MERIT Award, the National Institute for Diabetes and Digestive and Kidney Disease and the Center for Health Care Evaluation/Center for Innovation to Implementation.

Winkelmeyer is a member of the event adjudication committee for Medtronic, the data safety monitoring board for Medgenics and the scientific advisory boards of Amgen, Bayer, GlaxoSmithKline, Keryx, Mitsubishi-Tanabe and Rockwell. Stanford’s Department of Medicine also supported the work.

Becky Bach is an intern at the medical school’s Office of Communication & Public Affairs.

Awards

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a look at the heartbreaking and scarce medical resources on an Indian reservation in South Dakota, by Tracie Whitmer, a native of Rapid City, South Dakota.

CASE is a professional organization for those in the fields of communications, alumni relations and development at educational institutions. It includes more than 3,600 colleges and universities, as well as independent elementary and secondary schools in 82 countries. To recognize the best work in these fields, CASE sponsors its annual Circle of Excellence Awards.

Bronze for blog

Additionally, the Health Information Resource Center (a clearinghouse for professionals in the consumer–health field) gave a bronze award to Scope, the blog produced by the Office of Communication & Public Affairs. The center’s Web Health Awards were created to “recognize high-quality electronic health information.” Scope attracts more than 70,000 readers each month, and is overseen by Michelle Brandt.

Please give blood

Blood type needed: O+, A-, B+

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Stanford Blood Center

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Sutures allow baby — and his parents — to breathe easy

By Diana Walsh

Elizabeth Rodriguez-Garcia was nearly six months pregnant and in a celebratory mood when she went in for a routine ultrasound in July 2013. It would be the first baby, a boy, for Rodriguez-Garcia and her husband, Salvador Alvarez.

But something was wrong. The ultrasound techni-
cian found a large, dark spot where the fetus’s left lung should have been. The family was immediately referred to Stanford Children’s Health Perinatal Diagnostic Center in Salinas. Although Rodriguez-Garcia was still 80 miles away from Lucile Packard Children’s Hospi-
tal Stanford, a group of experts at the hospital’s Center for Fetal and Maternal Health was already examining a transmission of her ultrasound images and medical records.

“Even before all of us met face-to-face, we had many meetings to review the ultrasounds, the literature and our experience, and to formulate a plan,” said Susan Hintz, MD, the center director and professor of neona-
tology at the School of Medicine. The fetus had a con-
genital pulmonary airway malformation, which meant he had a large, abnormal cyst in the lower left side of his lung.

The fluid-filled cyst was not only impeding growth of the lung but also compressing his esophagus and

pushing on his heart. Worse, a new ultrasound showed that the cyst had grown even larger and that the fetus was at high risk of dying in utero. The doctor’s instinct known as hydrops. He was at high risk of dying in utero. The doctors told the parents that a fetal intervention, which involved inserting a shunt to the fetus and draining the cyst, would offer the baby the best chance of survival. A week after the cyst was discovered, Jane Chueh, MD, director of prenatal diagnosis and therapy at the hospital’s Johnson Pregnancy and Newborn Center, inserted a large needle into Rodriguez-Garcia’s abdo-

men and into the fetus’s chest in ultrasound guid-
ance, then threaded a small rubber shunt through the

needle into the cyst. “It immediately started to drain,” Chueh said. “It’s like popping a water balloon. Most of the fluid came out in seconds.”

Relieving pressure from the cyst came at a critical
time, said Chueh, a clinical professor of obstetrics and gynecology at the School of Medicine.

“As Rodriguez-Garcia got closer to due date, Hintz and the medical team discussed the next step — this one for delivery. Though the fetus was doing well, ultrasounds showed that once he was born, the cyst might need to be removed by emergency surgery to al-

low him to breathe properly.

“To simplify the transition between delivery and sur-

gery, a C-section was performed in an operating room

on Nov. 25, when Rodriguez-Garcia was 39 weeks preg-
nant. A large team of surgeons, obstetricians, anesthesi-
ologists, neonatologists and respiratory therapists were

on site to respond immediately to save the life of the

baby, who could have significant breathing problems.

Within minutes of birth, the baby was moved into another operating room, where the team, led by Karl Sylvester, MD, executive director of the Center for Fetal and Maternal Health and associate professor of surgery, along with Matias Bruzoni, MD, assistant professor of pediatric surgery, removed the cyst and more than two-

thirds of the baby’s lung that was adversely affected by the
cyst.

The baby, named Elijah, went home to Salinas on

Christmas Eve, after a month in the hospital. While it’s

still too soon to tell what the long-term effects will be,
doctors say his path so far is encouraging. Until a child

is about 7, lungs continue to grow, so there is a good

chance that Elijah’s lungs will develop to a normal size.

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Diana Walsh is a freelance writer.