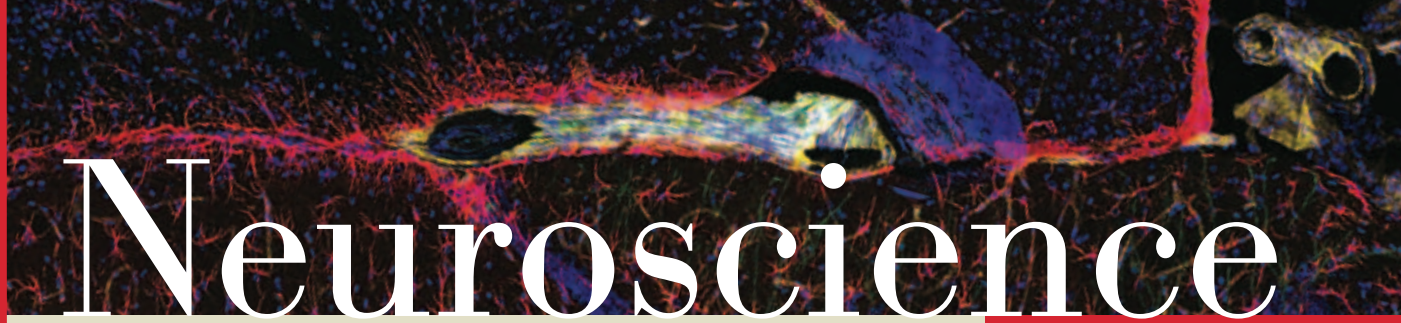
From the Bench



Neuroscience

CURRENT RESEARCH AT THE SALK INSTITUTE

SUMMER 2010

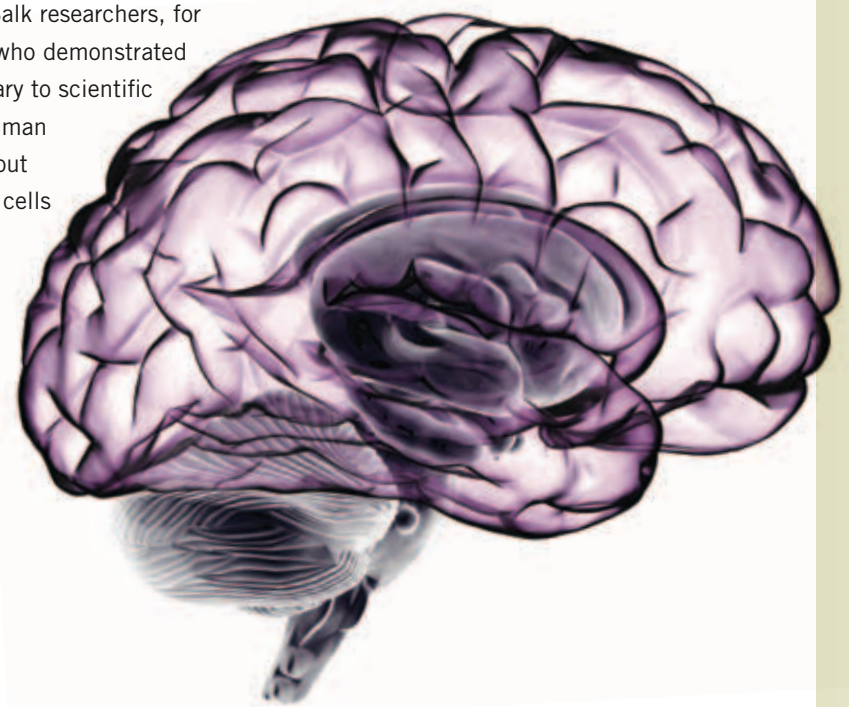
EVERYTHING WE ARE, ALL THAT WE HAVE been, all we will become resides in one remarkable organ—the brain.

THE BRAIN IS OUR BODY'S CENTRAL processor, controlling our behavior, our organs, and virtually all our bodily functions and activities. It governs body temperature, heart rate, blood pressure, and breathing. It facilitates speech and locomotion; processes thinking, emotions, and imagination; and allows us to interpret sensory inputs from the world around us. But the brain's very complexity has prevented scientists from understanding its physiology and function to the same degree that they understand other organs.

Since 1964, when the Salk Institute sponsored the first neuroscience meeting on the Torrey Pines mesa, Salk scientists have been probing the brain, making groundbreaking discoveries that have significantly advanced our knowledge of the body's master controller.

It was Salk researchers, for instance, who demonstrated that contrary to scientific dogma, human brains sprout new nerve cells throughout life. They also discovered that the left hemisphere of the human brain is specialized for languages, whether spoken or signed; identified the brain's central switchboard, which mediates the body's responses to stress; elucidated specific receptors that are crucial for learning and memory formation; and launched the neural networks revolution in computing. Because of research like this, Salk has repeatedly garnered the top spot in international rankings in the "Neuroscience and Behavior" category by *Science Watch*, an organization that measures the citation impact of scientific research published worldwide.

Neuroscience remains a major ongoing focus at Salk, and the following pages showcase some of our investigators' most recent—and insightful—work.



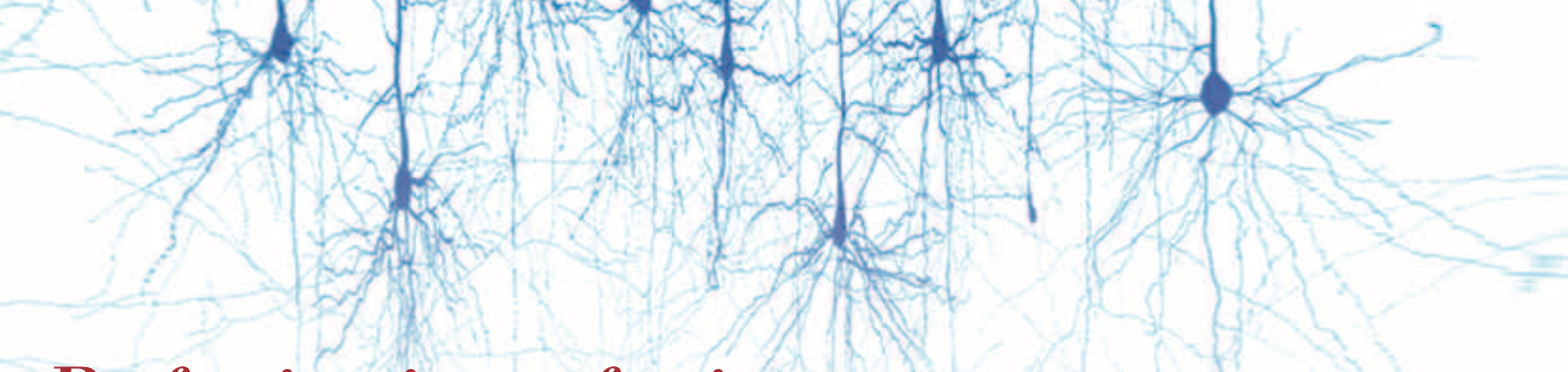
The Dynamic Brain Initiative

Unlike a computer's CPU, the brain is not a static machine with fixed and predetermined capabilities; it is dynamic in both form and function, constantly changing in response to our experiences and environmental stimuli. Every time we open our eyes, listen to music, drive a car, or kick a soccer ball, the electrical and chemical activities of billions of neurons and their connections are almost instantly altered. If sustained, every change will, in turn, affect gene expression and, eventually, the shape and function of our brain cells.

Over the course of a lifetime, this plasticity continually remodels our brain, resulting in learning, the formation of new memories, the acquisition of new skills and sometimes, when things go awry, the devastation of neurodegenerative and mental disorders.

Scientists have been studying the brain's architecture for more than a century, but they have barely addressed its dynamic nature, which has slowly become apparent over the past decade.

The Dynamic Brain Initiative, designed to facilitate the study of the living brain and how it changes over time, will usher in a new era in Salk neuroscience. Leveraging the latest technology and the Institute's existing strengths in interdisciplinary collaboration, it will bring together a cadre of people who will be the driving force behind future neuroscience innovation.



Perfecting imperfections

NEURONS IN THE RETINA ONLY RESPOND when a stimulus appears within an approximately round window covering a small part of the visual field that the eye sees. Theoretically, one would expect to obtain the best resolution if these windows, known as receptive fields, were circular and arranged on a perfect triangular lattice. Indeed, receptive fields are more or less circular and are positioned on a more or less triangular lattice, but imprecisely so. In collaboration with **Charles Stevens**, **Tatyana Sharpee** and her team were surprised to find that the combination of these two types of irregularities yielded a near perfect performance. By comparison, performance dropped by a third when receptive fields were either made perfectly circular or irregular receptive fields were adjusted to follow an ideal lattice.

These results suggest new strategies for improving the performance of retinal implants that could help restore vision in blind people. Retinal prosthetic devices rely on an array of electrodes, which is implanted near the retina to sent electrical signals to the brain through remaining neurons in the retina. Although the implants themselves are regular man-made arrays, irregularities arise at the interface with the neural tissue, in part because cells move from their original positions over time. The same algorithms that Sharpee and her colleagues used to predict receptive fields in a healthy retina can now be used to find the optimal outlines of the regions of visual space that should be associated with a particular electrode.

"Neuronal circuits in the brain, built from cells and the connections between them, cannot be made as regular as man-made systems. Yet animals can detect and act on signals in the environment with precision that rivals that of engineered systems." TATYANA SHARPEE

Rising above the din

THE BRAIN NEVER SITS IDLE. WHETHER WE ARE AWAKE or asleep, watching TV or sitting with our eyes closed, waves of spontaneous nerve signals wash through our brains. To be reliably processed, incoming sensory information has to stand out from this ongoing internal racket. Researchers had known for some time that paying attention to visual details increases the firing rate of neurons tuned for attended stimuli. The stronger the neural signal, the better we are able to perceive a stimulus. But neurons are very noisy computing devices, and even under the most controlled laboratory conditions, the responses evoked by identical, repeated stimuli vary from trial to trial.

If each neuron produced random noise that was independent from what its neighbor was doing, the brain cell on the receiving end could simply pool all incoming signals and average out the noise. But most of the brain's background noise originates in waves of spontaneous nerve signals and can't be simply averaged out. However, an interesting thing happened when **John Reynolds** and his team measured the activity of populations of brain cells in animals trained to play a video game that required rapt attention. When attention was directed to a visual stimulus on a computer monitor, the internal fluctuations or shared noise quieted down, increasing the salience of the incoming sensory information. This noise reduction substantially increased the fidelity of the neural signal, an improvement four times as large as the improvement caused by attention-dependent increases in firing rate alone.

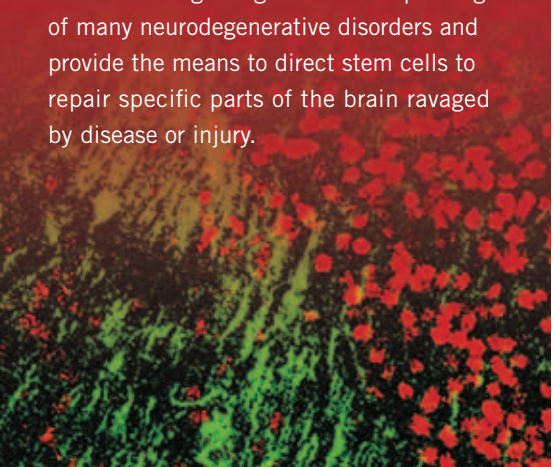
A hallmark of brain disorders such as Alzheimer's disease, autism, and schizophrenia is the loss of one's capacity to attend to relevant sensory information. This newly discovered neural mechanism has enormous implications for treating diseases in which attention fails, and the Reynolds laboratory is now embarking on a series of studies to understand how failures of this neural mechanism figure in brain disease.

Mind matter

THE CEREBRAL CORTEX, THE LARGEST and most complex component of the brain, is unique to mammals and alone has evolved human specializations. Although at first all stem cells in charge of building the cerebral cortex—the outermost layer of neurons commonly referred to as gray matter—are created equal, soon they irrevocably commit to forming specific cortical regions. But how the stem cells' destiny is determined had remained an open question.

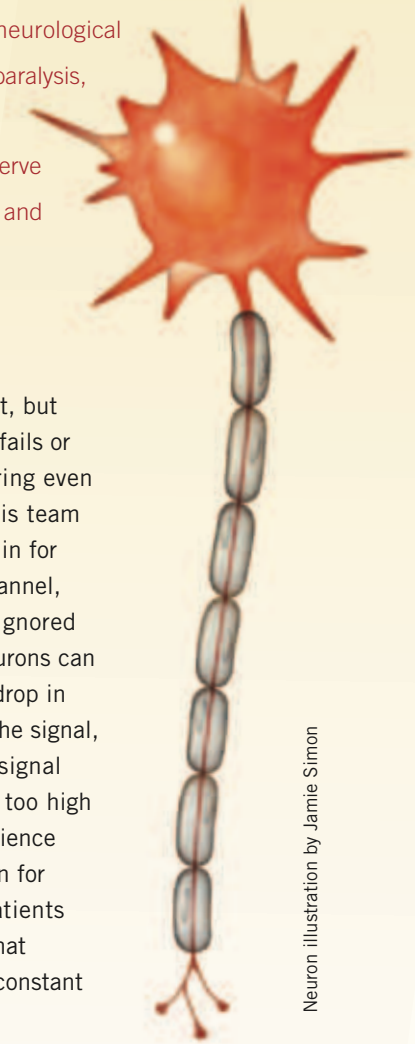
Early during neurogenesis, stem cell-like progenitor cells known as neuroepithelial cells undergo symmetric cell division to expand the pool of neuroepithelial cells. Later, they differentiate into more mature progenitor cells referred to as radial glia, which divide asymmetrically to produce a constant stream of both progenitors and neurons, the latter migrating outward to establish the gray matter of specialized cortical regions.

In an earlier study, **Dennis O'Leary** and his team uncovered that the growth factor Fgf10 controls the timing of the critical transition period that bridges the early expansion phase of neuroepithelial cells and the later neurogenic phase of radial glia. More recently, the researchers identified the first genetic mechanism that determines the regional identity of progenitors tasked with generating the cerebral cortex. Their discovery revealed a critical period during which a transcription factor known as Lhx2 determines the progenitors' regional destiny to generate either cortical regions that process olfaction, or regions that process the other senses—vision, hearing, and somatosensation. Once the window of opportunity closes, their fate is sealed. This knowledge will potentially help in understanding the genetic underpinnings of many neurodegenerative disorders and provide the means to direct stem cells to repair specific parts of the brain ravaged by disease or injury.



Multiple Sclerosis (MS)

AFFECTS AN ESTIMATED 400,000 AMERICANS AND MORE THAN 2.5 MILLION people worldwide. A chronic, often disabling disease that attacks the central nervous system, it is characterized by a baffling range of neurological symptoms, including numbness, tingling, motor weakness, paralysis, and vision loss. It is thought to result when the immune system attacks the myelin sheath that insulates axons, the nerve fibers that conduct electrical impulses to and from the brain and between neurons within the brain.



Neuron illustration by Jamie Simon

The model

Ordinarily, myelin speeds up the signals the axons transmit, but when axons lose their insulation, either signal conduction fails or axons become hyperexcitable and overcompensate by firing even in the absence of an input. When **Terry Sejnowski** and his team built a computer model simulating the disease, they were in for a surprise. They found that the ratio between a sodium channel, which initiates the electrical impulse, and a previously ignored but ubiquitous potassium channel determines whether neurons can fire properly. If the sodium level drops, an accompanying drop in the so-called potassium-based leak current will maintain the signal, whereas if the sodium drops but the leak current doesn't, signal transmission may fail. Conversely, if the sodium level is too high and the leak current doesn't increase, a patient may experience twitching. Sejnowski's model not only offers an explanation for many of the bizarre symptoms that multiple sclerosis patients experience but could also provide a new target for drugs that increase or decrease the potassium current to maintain a constant ratio and offer relief.

The treatment

Current treatments for MS focus on immunosuppressive therapies to decrease the number of attacks and slow the progression of the disease. Unfortunately, all of these treatments and particularly interferon beta (IFNß) have severe side effects, causing many patients to discontinue treatment. IFNß's onerous effects most likely arise from its immuno-stimulatory activity, while its beneficial effects on MS are thought to result from an immuno-suppressive action. **Greg Lemke**'s research on so-called TAM receptors could explain how the same molecule can exhibit both immuno-stimulatory and immuno-suppressive activities.

As part of the innate arm of the immune system, APCs, short for antigen-presenting cells, keep invading pathogens in check until T and B cells—which take a few days to mobilize—kick into full gear. When APCs encounter foreign intruders, they unleash a wave of chemical messengers that jumpstart the T and B cell response. When the trespassers have been successfully battled, the APCs go off duty, and T and B cell activity tapers off. Without TAM receptors, Lemke discovered, APCs never shut down. Instead, they remain in red-alert state, and over time, the ensuing chronic inflammation overwhelms the regulatory mechanisms that prevent our immune system from turning against our own body.

Lemke's research suggests that the IFNß used to treat MS cooperates with TAM receptors to put the brakes on inflammation. If that is indeed the case, IFNß therapy combined with TAM-specific drugs may lead to more efficacious and better-tolerated treatments to alleviate MS, Crohn's disease, and other autoimmune syndromes.

Forget about it!

POST-TRAUMATIC STRESS DISORDER, or PTSD, is an anxiety disorder that can develop after a terrifying ordeal in which grave physical harm occurred or was threatened. It affects approximately 5.2 million Americans, including as many as one in eight returning soldiers. But you don't have to be a combat soldier to develop PTSD; any bad experience in daily life will do. If traumatic memories persist inappropriately, sensory cues will trigger recall of the distressing memories and the associated stress and fear.

As a way of modeling anxiety disorders in humans, researchers train mice to fear a tone by coupling it with a foot shock. If this fear conditioning is followed by repeated exposure to the tone without adverse consequences, the fear will subside, a behavioral change called fear extinction or inhibitory learning. Inhibitory learning is thought to be a parallel learning mechanism that requires the acquisition of new information as well as the suppression of previously acquired experiences to be able to adapt to novel situations or environments.

Stephen Heinemann and his team were interested in whether a receptor called mGluR5, which had been shown to be involved in several forms of behavioral learning, also plays a role in inhibitory learning. To find out, they conducted a series of experiments with mice lacking the gene for mGluR5. What they discovered was that mGluR5-deficient mice had severe deficits in tasks that required them to "unlearn" what they had just learned. They believe that the same mechanism is perturbed in PTSD and that mGluR5 could provide a potential target for therapeutic intervention.

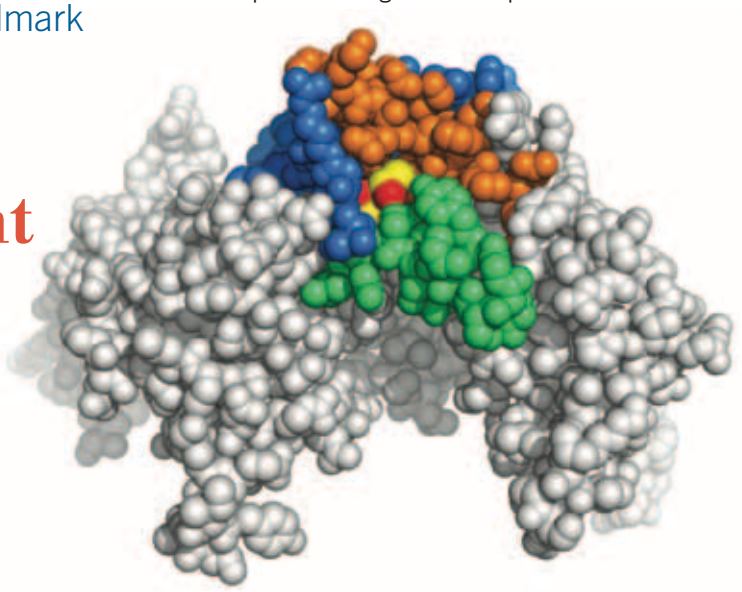
"Most people agree that failure to 'unlearn' is a hallmark of post-traumatic stress disorders."

STEPHEN HEINEMANN

Not just a social lubricant

ALCOHOL HAS A LONG HISTORY OF WIDESPREAD USE AND abuse, but when it comes to its impact on brain activity at a molecular level, it remains among the least understood of psychoactive drugs. Although alcohol had previously been shown to open a type of potassium channel *(GIRK)* that controls electrical activity in the brain, it was not known whether this was a direct effect or byproduct of other molecular changes in the cell.

In determining the three-dimensional structure of these channels at high resolution, **Paul A. Slesinger** and collaborators discovered a molecular pocket that held an alcohol molecule. Using this structural information, they systematically introduced amino acid substitutions that denied alcohol molecules access to the pocket and found that alcohol no longer efficiently activated the channel, confirming that they had hit upon an important regulatory site for alcohol. The team further established that the pocket is a crucial trigger point for the channel since G protein activation was also altered. They believe that alcohol hijacks the intrinsic mechanism for opening *GIRK* channels, perhaps by "lubricating" the channel's activation "gears."



A better understanding of how *GIRK* channels are activated could point to new strategies for treating human diseases. Using the protein structure as a starting point, for example, it may be possible to develop a drug that antagonizes the actions of alcohol to treat alcohol dependence. Alternatively, if a novel drug is identified that fits the alcohol-binding site and selectively activates *GIRK* channels, this could dampen overall neuronal excitability in the brain and perhaps provide a novel pharmacological tool for treating epilepsy.

In search of schematics

DOZENS OF DIFFERENT CELL TYPES work together in the brain in distinct networks. But the circuits are intermingled, and even neighboring neurons of the same type differ in connectivity and function. Without access to a map of the neuronal connections, attempting to grasp how the brain lets us understand language, recognize faces, and schedule our day is like trying to discern how a computer chip works simply by looking at it.

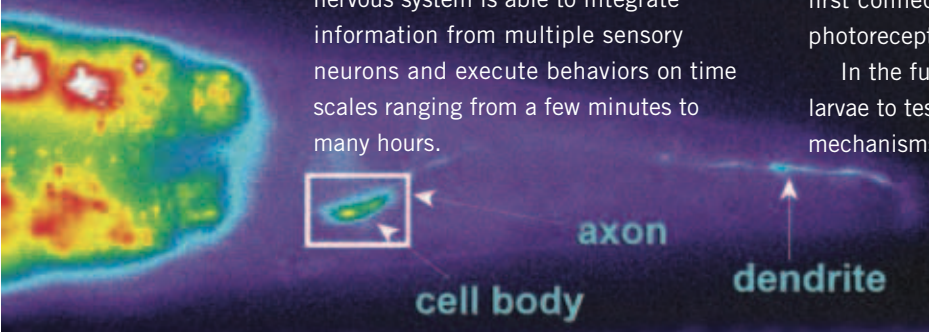
Recently, **Edward Callaway** and his group have jumped a major hurdle to preparing that "wiring diagram": figuring out single connections between neurons. They successfully modified the rabies virus, turning it into a tool that can cross the synaptic space of an infected nerve cell just once to identify all the neurons to which it reaches out. Viruses that naturally spread between neurons have previously been used to track nerve cell communication, but without a way to stop them in their tracks, over time, they will light up the whole brain.

Using these tools, they are now beginning to construct the wiring map as subsequent populations of cells are visualized. And once scientists can identify a neural circuit, they can then correlate it with such brain functions as perception and behavior.

Sniffing out dinner

OUR BRAIN IS A MARVEL OF EVOLUTIONARY ENGINEERING, allowing us to navigate an ever-changing environment, learn, and remember, but its stunning complexity makes it difficult to trace how information travels from one neuron to another.

Sreekanth Chalasani uses the nematode *Caenorhabditis elegans* as a model to understand how neural circuits transform sensory input into behaviors. *C. elegans* has 959 adult somatic cells and 302 neurons connected by 6,000 electrical and chemical connections. Despite its simplicity, it displays a number of sophisticated behaviors, making it a perfect model to explore how a well-defined nervous system is able to integrate information from multiple sensory neurons and execute behaviors on time scales ranging from a few minutes to many hours.



Wild-type worms spend about 15 minutes searching a local area for food when they are moved from food to a food-free plate. The duration of this search depends on the quality of the food and the amount of time they have spent feeding on it before being moved (more nutritious food or longer times elicit longer searches and vice versa). Chalasani found that the worms' main olfactory neurons are primarily responsible for this food-seeking behavior. They are activated upon removal of a stimulus and respond by releasing chemical signals, which in turn activate one target neuron and inhibit a second target neuron. These opposite connections resemble the first connections in the visual processing system in our eyes—photoreceptors connecting to "On" and "Off" bipolar cells.

In the future, Chalasani plans to extend his studies to zebrafish larvae to test whether vertebrate and invertebrate circuits use similar mechanisms to process information.

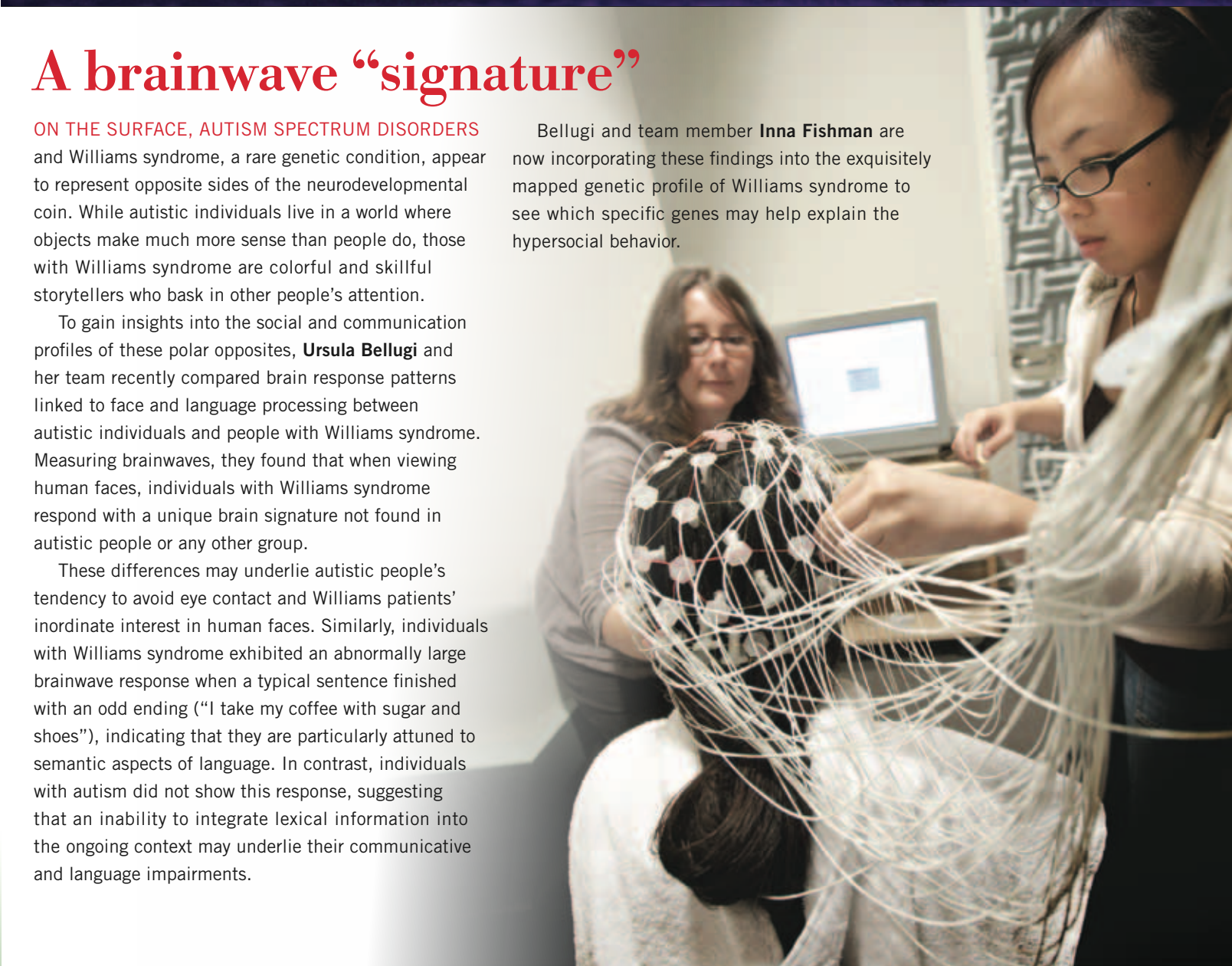
A brainwave "signature"

ON THE SURFACE, AUTISM SPECTRUM DISORDERS and Williams syndrome, a rare genetic condition, appear to represent opposite sides of the neurodevelopmental coin. While autistic individuals live in a world where objects make much more sense than people do, those with Williams syndrome are colorful and skillful storytellers who bask in other people's attention.

To gain insights into the social and communication profiles of these polar opposites, **Ursula Bellugi** and her team recently compared brain response patterns linked to face and language processing between autistic individuals and people with Williams syndrome. Measuring brainwaves, they found that when viewing human faces, individuals with Williams syndrome respond with a unique brain signature not found in autistic people or any other group.

These differences may underlie autistic people's tendency to avoid eye contact and Williams patients' inordinate interest in human faces. Similarly, individuals with Williams syndrome exhibited an abnormally large brainwave response when a typical sentence finished with an odd ending ("I take my coffee with sugar and shoes"), indicating that they are particularly attuned to semantic aspects of language. In contrast, individuals with autism did not show this response, suggesting that an inability to integrate lexical information into the ongoing context may underlie their communicative and language impairments.

Bellugi and team member **Inna Fishman** are now incorporating these findings into the exquisitely mapped genetic profile of Williams syndrome to see which specific genes may help explain the hypersocial behavior.



Involuntary maybe, but certainly not random

OUR EYES ARE IN CONSTANT MOTION. Even when we attempt to stare straight at a stationary target, our eyes jump and jiggle imperceptibly. For several decades, scientists have debated the function, if any, of these unconscious flicks, also known as microsaccades. Wondering whether the command center responsible for generating these quick darts resides within the same brain structure that controls our eyes as we scan the lines in a newspaper or follow a moving object, **Richard Krauzlis** decided to measure neural activity in the superior colliculus before and during microsaccades. The superior colliculus is an evolutionary conserved brain region that helps orient the head and eyes either toward or away from the sights and sounds in our environment.

Krauzlis and his team not only discovered that the superior colliculus is an integral part of the neural mechanism that controls microsaccades, but also found that individual neurons in the superior colliculus are highly specific about which particular directions and amplitudes they command—even for these smallest of detectable eye movements, which redirect our line of sight by about the width of a sewing needle held at arm's length. Because images on the retina fade from view if they are perfectly stabilized, discovery of this mechanism explains how the central nervous system generates these miniature movements to constantly shift the scene ever so slightly, thus refreshing the images on our retina and preventing us from going "blind." Microsaccades, however, do more than prevent the world around us from fading from view. When we avoid looking directly at an object of interest—for reasons of propriety, for example—our microsaccades reveal such objects of attraction because their direction is biased toward the object.

An expert's eye

WE LIVE IN A DYNAMIC AND EVER-CHANGING ENVIRONMENT. Optimal encoding of sensory information requires that sensory systems be continuously recalibrated to make the most of the prevailing environment, much like fine-tuning your car for the current driving conditions. But just how the brain achieves this feat has been unclear. One way to test this recalibration hypothesis is to ask people to scroll through the color spectrum till they arrive at "unique yellow"—yellow that can be described as containing neither a tint of red nor a tint of green. Surprisingly, in 99 out of 100 trials, people will pick exactly the same wavelength of 578 nm. However, if they spend a couple of hours in a greenish or reddish environment before the test, their perception of unique yellow will shift up or down a few nanometers.

Humans and closely related primates perceive color through three types of photoreceptors—red, green, and blue—all of which send their information through the so-called color opponent system. The red/green channel determines the relative amounts of red versus green, while the blue/yellow channel does the same for blue and yellow. This system allows the brain not only to tell the difference between the two colors but to finely discriminate colors that fall between the two extremes. Unique yellow represents the exact balance point between red and green.

By measuring neuronal activity, **Thomas Albright** and his team discovered that a color-biased environment shifts the weight given to one of the two opposing colors, not only explaining the observed shift in the wavelength of the color perceived as unique yellow but also how the brain's sensitivity can be geared toward one end of the red/green color spectrum. These observations reveal that sensory processing is markedly adaptable and help explain the phenomenon of "sensory expertise," in which individuals develop extraordinarily fine sensory discriminatory abilities.

Photo courtesy of Alban Karlseder

This issue of *From the Bench* is part of a series of updates on key areas of scientific research conducted at the Salk Institute for Biological Studies. Our goal is to keep you informed of Salk researchers' most recent findings in areas such as stem cells and regeneration, vision, plant biology, neuroscience, behavior, and more. We are very interested in your feedback regarding this update.

For more information, or to share your comments, please contact Judy Hodges at the Institute's Office of Development at 858.453.4100 x1882 or email hodges@salk.edu.

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