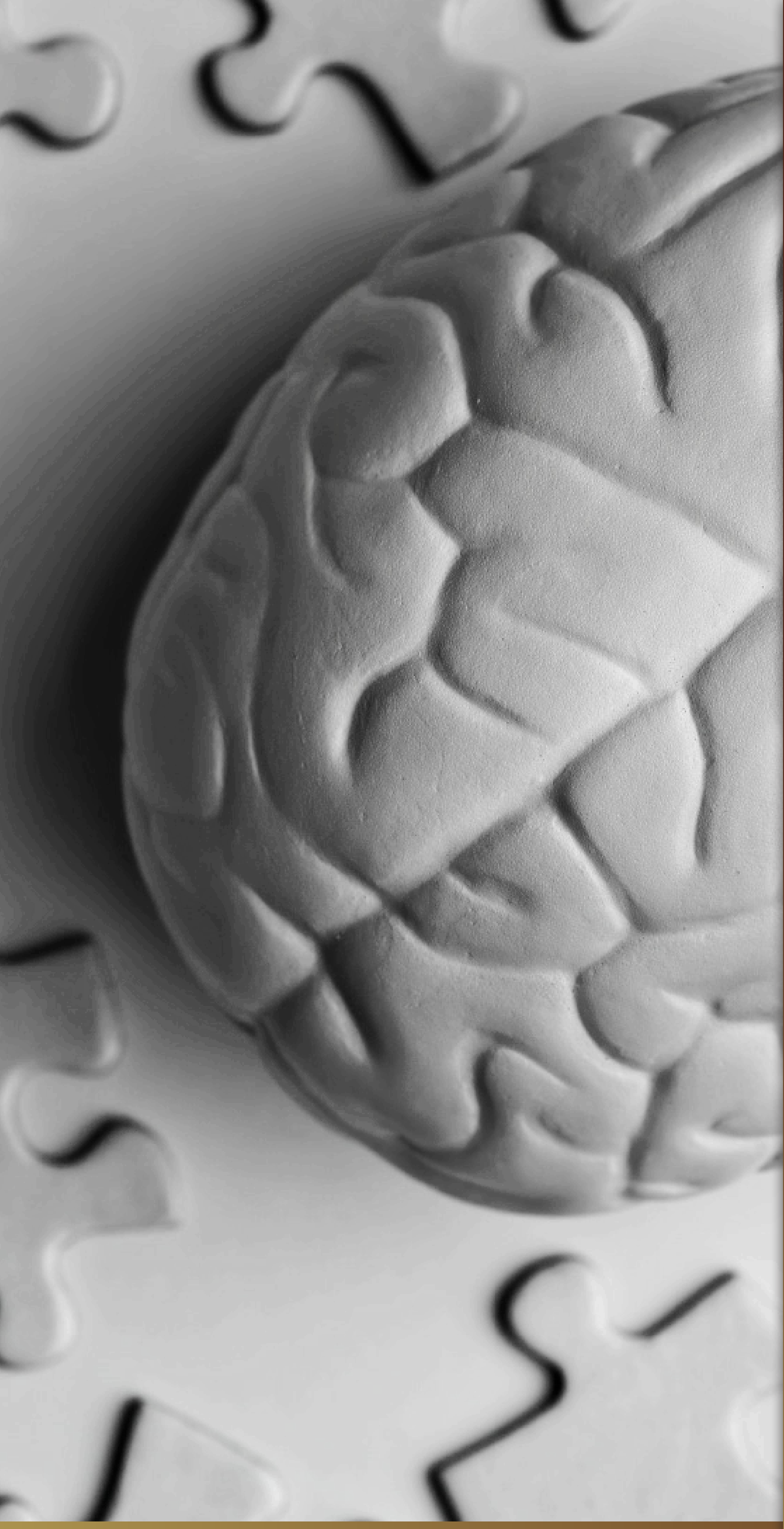

Solving Mysteries of Autism via The Power of Collaboration

Dr. Guido Gerig
Early-Brain Development Research Reveals Vibrant Clues

UCNiA

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Photo: Bryan Jones

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The glossy whiteboards that line the walls in offices, lounge areas, and conference rooms are one of the first things Guido Gerig, PhD, noted when the University of Utah's Scientific Computing and Imaging (SCI) Institute first began courting him to join their team in 2007. For someone so prominent worldwide for his image analysis expertise and seminal research, whiteboards seemed the simplest of visual tools. Yet, what these signaled to Gerig was that this place fostered collaboration among students, postdocs, and faculty; these ubiquitous boards were an immediate means to visually improve understanding and share knowledge.

Pencil in hand, Gerig fills three pages with a whirl of sketches as he explains how his imaging work illuminates clinical findings in his research involving early brain development, and more specifically autism. The sketches fade to stick figure-status as Gerig jumps back and forth between the paper and the color-exploding images on his computer screen. Vivid and seemingly pulsating with life, the brain-development images are a result of thousands of highly precise, quantifiable measurements never before captured visually.

Immersed in solving a mystery, Gerig and his multi-disciplinary team from across the United States and Canada are finding clues that could ultimately and dramatically improve the lives of children with autism and their families. It is also advancing research in other areas such as Parkinson's disease, Huntington's disease and Alzheimer's disease.

"Scientists Have Long Wondered If Problems in the Brain Start Earlier"

"You will see four-dimensional imaging analysis in our longitude studies. Time is the fourth dimension," says Gerig, whose English is couched in a soft-spoken Swiss-German accent. He is referring to the Infant Brain Imaging Study (IBIS), part of the Autism Centers of Excellence Program. "This is unique; it is the first large study where you can measure changes over time in early brain development."

Funded by the National Institute of Health, the study focuses on identifying infants most at risk for developing autism and the prospect of offering early intervention. Through IBIS, Gerig works with colleagues based at five other sites, whose expertise includes psychiatry, psychology and radiology. One of the sites, the University of North Carolina (UNC), also provides image analysis expertise using processing of magnetic resonance imaging (MRI). Gerig's team at the SCI Institute focuses on using Diffusion Tensor Imaging (DTI) to provide three-dimensional images that show changes over time in each infant's white matter fiber bundles and connectivity (the pathways connecting brain regions).

"I'm part of a big puzzle of collaborators who all have to work together in order to find answers," says Gerig, who often follows his knowledgeable explanations of the brains inner-workings or the nuances of autism with a humble dismissal, "but neuroscience is not my area of expertise, you must ask the experts."

Yet, it is clear Gerig approaches his work with a breadth and depth of understanding of these other areas involved in IBIS. "As part of this multidisciplinary team, I have to go beyond just understanding my own area of expertise; I have to know what measurements are important to those bringing in the neuroscience and psychiatric expertise," says Gerig, who is also a Professor of Computer Science within the University of Utah's School of Computing. "We are *more* closely connected than a series of overlapping Venn diagrams."

"To be a cutting edge researcher in our field, you have to be interested not just in doing the computer science work, but trying to understand the next level and how what you are doing translates over to the next level, in our case [the] application-to-autism level," explains Martin Styner, PhD MS ETH, who runs the Neuro Image Analysis and Research Lab at UNC and is an IBIS collaborator. "You have to have the interest and drive to create the method and understand the application to autism and neurodevelopment studies."

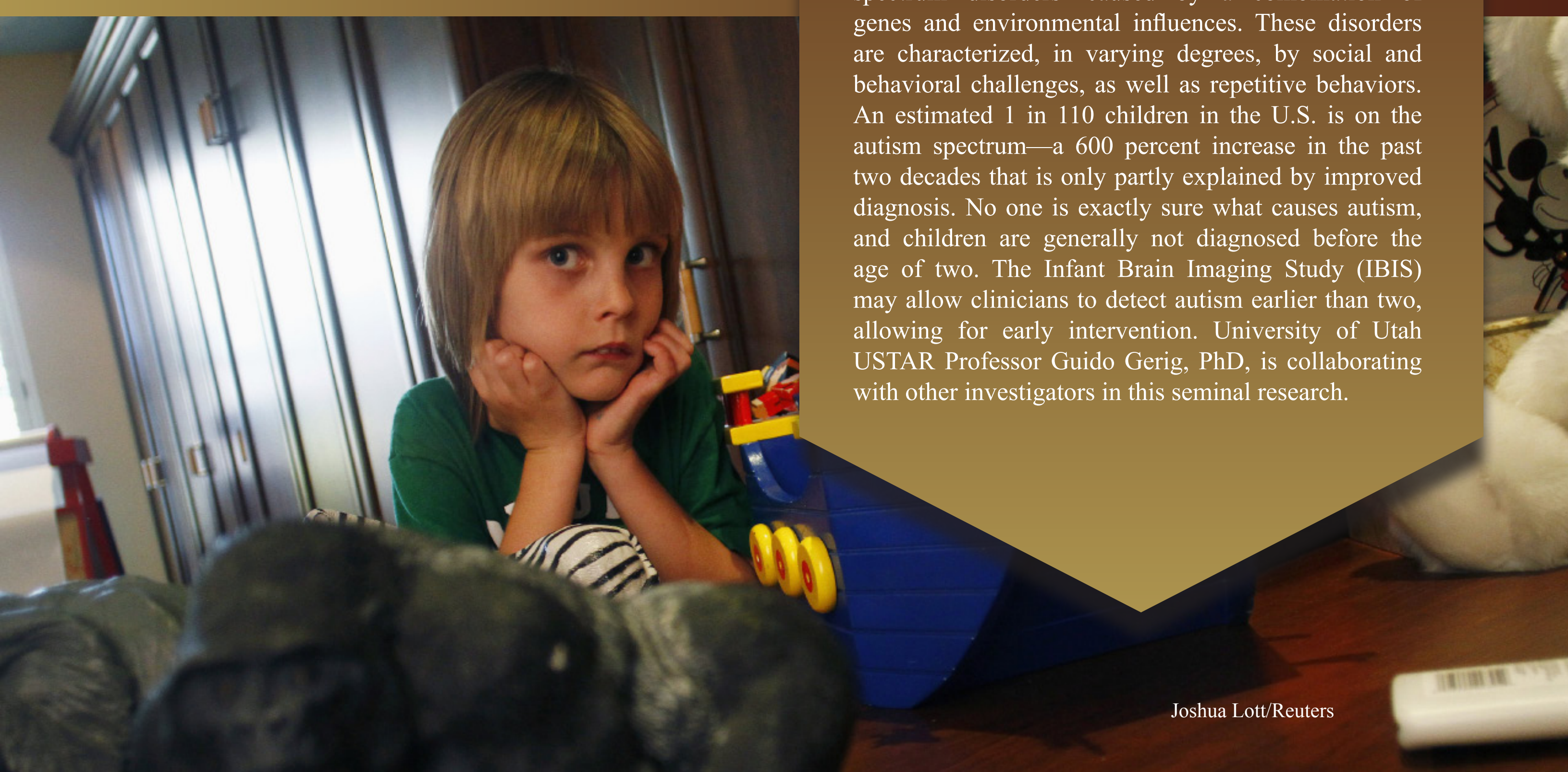
The study, first published in the *American Journal of Psychiatry* (June, 2012), found that children who develop autism have abnormalities on brain scans that can be detected long before obvious symptoms advance. Children with autism are rarely diagnosed before the age of two. The study followed 92 infants from six-months through two-years old. (Brain scans were conducted at 6 months, one year, and two years of age). The infants that were considered high risk had a sibling with autism, which puts their risk for autism at 25 percent. Twenty-eight of these infants were eventually diagnosed with the disorder.

A special type of MRI scan (DTI) showed developed nerve connections of a normal brain. When compared to a scan of a brain of an infant with autism, the pattern is significantly different. This study allowed scientists to detect differences in the brain connectivity by six months of age in the children who went on to develop autism. At two years of age, these children also had enlarged brains compared to infants the same age who did not develop autism. An infant's brain is rapidly evolving during the first two years of life, literally doubling in size the first year.

While cognitive development can be assessed early on in infants, it has not been done with the brain. This study breaks new ground, allowing for the opportunity to find the seed of the disorder before it has fully taken root. Early diagnosis is crucial; research suggests the symptoms of autism—problems with communication, social interaction and behavior—can improve with early intervention. As scientists better understand what causes autism, it may eventually open the door for more effective treatment or even prevention.

Autism Spectrum Disorder

Autism is a general term used to describe a group of complex developmental brain disorders—autism spectrum disorders—caused by a combination of genes and environmental influences. These disorders are characterized, in varying degrees, by social and behavioral challenges, as well as repetitive behaviors. An estimated 1 in 110 children in the U.S. is on the autism spectrum—a 600 percent increase in the past two decades that is only partly explained by improved diagnosis. No one is exactly sure what causes autism, and children are generally not diagnosed before the age of two. The Infant Brain Imaging Study (IBIS) may allow clinicians to detect autism earlier than two, allowing for early intervention. University of Utah USTAR Professor Guido Gerig, PhD, is collaborating with other investigators in this seminal research.

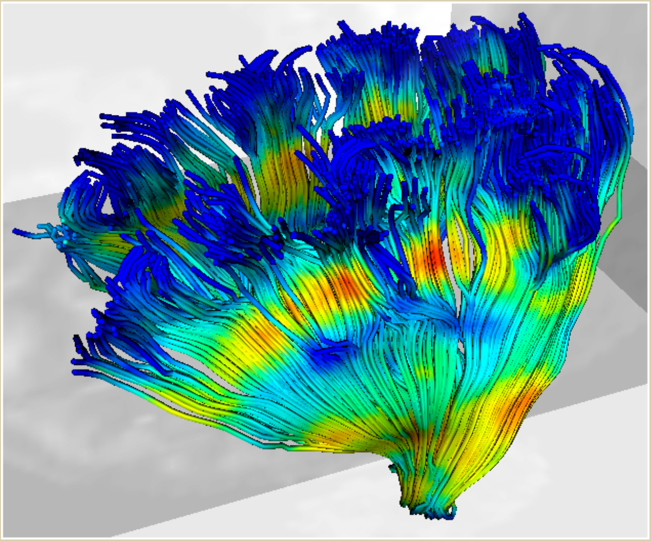


Joshua Lott/Reuters

“This is the only study that studies high-risk babies and follows them over time,” points out Gerig. “We want to be able to diagnose autism as early as six months. The focus right now is early detection.” It is not just advancing science that has motivated Gerig in his 14 years researching autism and early brain development; it is also his ability to empathize with those on the frontlines of the disease.

“If a child is diagnosed earlier, it helps the whole family. If a mother says to a doctor or school administrator, *‘my child is different and I need some help,’* then help is slow to come. If a parent is able to say, *‘my child is autistic,’* well then people step up to help and there is support,” says Gerig, whose gentle and patient nature makes it easy to imagine him comforting a baby, which he certainly has done as a father of two grown children. “The future is life-long for a baby; our progress can have a big impact on a child, a family, and society.”

Identifying autism before a baby is walking also bolsters the prospect of individualized therapies and may also provide insight into how autism presents itself differently among different populations.



This streamline visualization illustrates part of the white matter fiber connectivity of the human brain measured by diffusion tensor magnetic resonance imaging (DT-MRI). Shown here are projection tracts which extend vertically from the brain stem to the cerebral cortex, and carry information such as motor signals from the brain cortex to the spinal cord. The color coding indicates local structuring of connections, ranging from red (densely structured) over yellow and green to dark blue (diffuse fine scale).

Revealing the Brain as a World Atlas

Gerig’s office looks out on the Wasatch Mountains, one of a number of perks that made Salt Lake City enticing, helping convince him and his wife, Maya Gerig, PhD, to move from Chapel Hill, North Carolina. “It’s the East verses the Wild West,” quips Gerig who grew up skiing the Alps and now skis Alta.

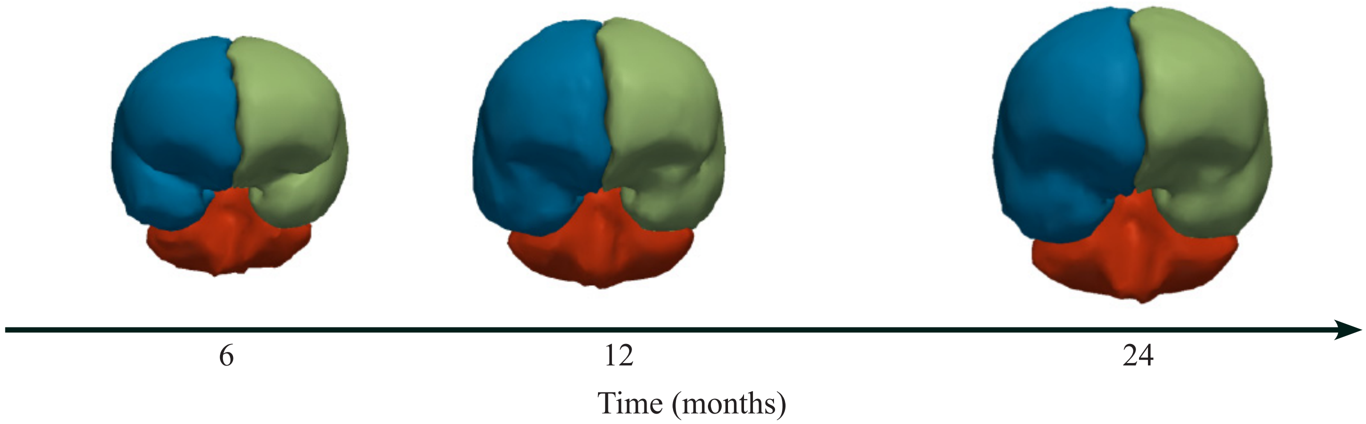
On his computer screen is a sharp, close-up image in various shades of black and white. Like a piece of abstract modern art, Gerig explains that the image is actually an acoustic lens. A music buff, whose taste range from Indian Classical to Italian Opera, Gerig says that an acoustic lens produces perfectly calibrated music. It creates music precisely as if it was being played live. A long-time violin player, Gerig can hone in on off-tune music like an editor zeroing in on typos. His eyes are

USTAR

A Catalyst for Innovation

Utah Science Technology and Research Initiative (USTAR) is a state-funded, long-term effort to strengthen Utah’s “knowledge economy,” creating high-paying jobs and new businesses. This bold initiative, created by Governor Huntsman and the Utah Legislature, invests in world-class innovation teams and facilities at the University of Utah and Utah State University, then works with the universities to commercialize the technologies through new business ventures across the state.

Sorenson Molecular Biotechnology Building



Brain growth from age 6months to 24 months shown at three discrete time points. Blue and green illustrate right and left brain hemispheres, and red the cerebellum. It is interesting that growth from 6 to 12 months is at least as large as from 12 to 24 months, indicating very strong growth very early in life which flattens off.

as discriminating as his ears. With a background in photography, Gerig taught university-level technical photography courses. "Photography now has the digital range of film but not the dynamic range as in valuations of light to dark," explains Gerig. Precision, calibrations, and visual quality are all arteries that pump real-life applications into his imaging processing and analysis.

Gerig and his five graduate students work together at turning raw, black-and-white radiology images into images that convey the evolving changes within the brain. They begin with an analysis of structure and segmentation—an anatomical view. They then divide an image into meaningful components, subdividing it further into specific regions, then tissue types (i.e., grey matter, white matter, fluid).

"Breaking our analysis of the brain down with all its multiple parts is a bit like looking at a world atlas; you see the whole world, then the continents and oceans, then countries, then states, cities, rivers, lakes," says Gerig. An apropos analogy, considering some images actually resemble satellite views of Earth. It is also a striking irony, when you consider the mysteries of the brain are as great as the mysteries of the universe, yet they reside deep within us. It is our mind, imagination, conscience and every function of our body. The brain is the center of the nervous system.

For Gerig, producing algorithms calculates the "geography" of the brain (volume, shape, thickness, size, etc.), then he produces numbers and value statistics to show clinicians what would be considered "normal," and variations from normal, in brain development. Preliminary conclusions are drawn from the brain image analysis and then passed on to clinicians for their take on it.

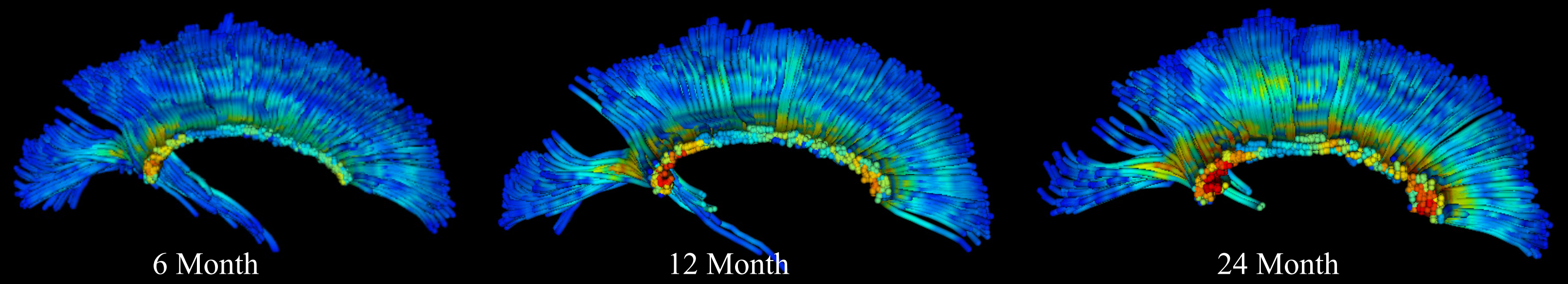
"We can also measure connectivity of the brain and develop technology to measure the maturity of the brain in regards to these connections. Electrical signals transmit faster with maturity," adds Gerig, who clicks on an image that resembles a burst of colorful plumage. The image measures longitude maturation. Gerig searches out another image, this one echoing the cosmos. Yet, this other world is a trajectory of the brain at 1 week, 3 months, 1 year, 2 years, 10 years.

"He's sort of a magician," says psychologist Heather Hazlett Cody, PhD, who has long collaborated on research projects (IBIS included) with Gerig. "He uses his expertise to problem solve for our group." She recalls when they first began research with two-year olds a decade ago all the imaging tools were designed for adults, and didn't really work properly with brain scans of toddlers. "We couldn't just plug what we had into the software, so Guido and his group created a whole set of new tools optimized for processing a young brain, so we could do what we needed to do."

Beneath the Cloak of Color are Clues

Despite the aesthetic appeal, the color coding is purely functional; it represents structural differences and helps explain the neurobiology of the brain. For example, volume loss of one group can be coded in blue whereas volume growth is in yellow. In addition, the results of statistical hypothesis tests are color-coded in order to show which regions are significantly different. For fiber bundles (the brain's pathways), researchers can display the three-dimensional geometry of major bundles and color-code them by anatomy as well as by the amount of structuring/maturation. Color can also signify velocity of brain growth—red is high speed, blue is zero growth. This colorful display of information allows other researchers and clinicians to more quickly understand and implement the information.

Dr. Gerig with students Neda Sadeghi and Anuja Sharma.



Brain maturation illustrated by changes of white matter brain connectivity and fiber tract structuring. Imaging infants with diffusion tensor magnetic resonance imaging (DT-MRI) at ages 6, 12 and 24 months clearly shows that maturation is not only expressed as change of size but also by increased fiber structuring, a process is called myelination. Streamlines shown in red indicate very strong structuring, whereas dark blue shows locations where fiber bundles disperse into folded cortical regions. The images demonstrate the right part of the commissural tract cropped the c-shaped corpus callosum, which is the major fiber bundle that enables the left and right brain hemispheres to communicate.

"The IBIS discoveries are a result of a mix between technology, new methodologies, and data that came available," says Gerig, noting that ten years ago the technology for calibrations was unavailable to do what they are doing today. To ensure accuracy, all four image acquisition sites involved in IBIS use the same MRI scanners and imaging instruments, which collect massive amounts of information. It is up to Gerig to make sense of this data and create tools, such as software systems, to extract the necessary information.

Up to this point, 30 percent of Gerig's and his team's research time is spent on calibration to ensure accuracy and quality; this provides a solid foundation for the study as it advances over the next five years. While Gerig admits that there is no measurement technique without any error, they try to keep the variability of measurements due to errors as small as possible, in order to detect even small differences due to conditions (i.e., fever, overweight). If devices are not calibrated, there is a large error margin for measurements which may completely hide differences which they want to identify. "I would compare it with the precision of any type of measuring device used at multiple places, such as a scale for weight measures or a thermometer for temperature." Calibration in the IBIS study is performed by scanning calibration patterns of known size, and by sending IBIS staff members to the four imaging sites to compare their brain scans.

A Boy's Curiosity is Fertile Ground for Innovation

A mind for how things work was apparent in Gerig as a boy growing up in a small Swiss town on the edge of Lake Constance (*Bodensee*) and in the shade of the Alps. He spent much of his time repairing things in the small apartment he shared with his three brothers (including his twin) and his parents. He took apart clocks, watches, vacuums, radios—anything that needed repairing—in order to understand how they functioned. With little money to spare on hobbies or wants, Gerig found his own pocket money by working odd jobs. One summer he cleaned windows in a piano factory; by the time he was done, young Gerig knew how pianos were built. "I would observe each step, as I went to clean windows in each room, until I understood how you end up with the final product," recalls Gerig. "It was my curiosity that made me want to learn what was going on around me."

His affable nature may have been further nurtured when he worked as a "postman" delivering mail and newspapers throughout his village. "Everyone knew me, but they knew me also because my father was a teacher at the elementary school."

When Gerig discovered his father's Agfa roll film camera at 12, he began teaching himself photography; it became a pursuit that fed his fascination with all things mechanical and technical. He eventually saved enough to build his own darkroom. Later, these skills earned him a teaching job at the same university he attended, helping him pay for his schooling and living expenses. While completing his master's in electrical engineering, the whole field of research in imaging was going digital. This awakened Gerig's interest in digital image processing, and he entered the field of image data analysis with his PhD research in Electrical Engineering & Computer Science.

"From A Science Perspective, We Cannot Exist Alone"

"Being directly at the interface of computer science, software engineering, and the medical field, we are always dependent on people wanting to work with us. Otherwise, we cannot exist from a science perspective, as medical image analysis is inherently collaborative," says Styner, who was mentored and taught by Gerig at the Swiss Federal Institute of Technology in Zurich (ETHZ) and later at UNC. He jointly analyzes the data for IBIS with Gerig, focusing on the structural image analysis.

Gerig's expertise as well as his approach to people and projects lends itself to collaboration. Effectiveness to create powerful change in lives only works in combination with the other experts involved," says Gerig, who agreed to come to Utah as long as he could continue working with UNC and the projects he had begun there. "Collaborations help build momentum in research," he adds. Fortunately, the collaborative nature of the SCI Institute culture was in alignment with Gerig's *modus operandi*.

His students are some of his biggest fans when it comes to how Gerig likes to do things. The recipient of four teaching awards, Gerig models what he expects from his students and is a living example of The Golden Rule. "Guido has a way of diffusing tension. I've never seen him get mad or annoyed, he approaches everything very diplomatically," observes James Fishbaugh, a graduate student working on brain shape-growth modeling. Fishbaugh gratefully recalls that during presentations, Guido will ask a question as if curious, when really he is guiding Fishbaugh to catch a point he had missed.

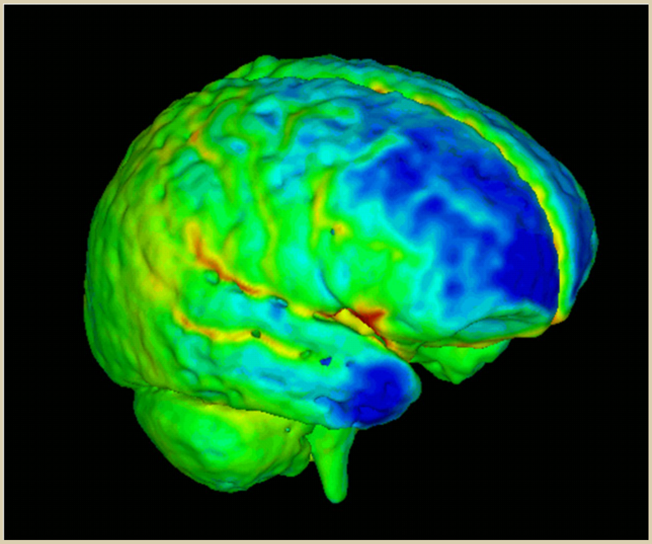
"You often find people in research who are brilliant but not good communicators," says graduate student Avantika Vardhan, who works on structural imaging changes with age. "Guido can speak both languages—that of the computer scientist and mathematicians, as well as the neuroscientist and clinicians." She describes Guido as a mentor who "quietly observes his students and shows them the way without being overbearing."

His sincerity toward people also shows up in his research. "He feels responsible, and this trickles down to his students. If he doesn't take shortcuts, then we don't take shortcuts," says graduate student Anuja Sharma, who researches brain connectivity changes with development. "He always relates back to the real world, reminding us not to just stick to our text books, but that we need to do research that is actually meaningful," says Sharma. "He has ingrained in me that the questions we are trying to answer will influence a clinician's judgments and, in turn, the patients. This will always stay with me as I continue my research."

It was Gerig's reputation as an international leader in medical imaging technology development that caught the attention of the SCI Institute and the Utah Science Technology and Research Initiative (USTAR). His position is funded by USTAR. Since he began his research in 1985 at ETHZ (a.k.a. the "MIT" of Europe), he has conducted a large number of national and international projects with close multidisciplinary collaboration between medicine, engineering, statistics, industry, and computer science. Several months were spent as a Visiting Assistant Professor at the Brigham and Women's Hospital at Harvard Medical School.

"The consensus of our image analysis experts and those from around the world was that one of the best image analysis researchers in the world, especially applied to neuroimaging, was Guido Gerig," says SCI Institute Director Chris Johnson, who helped recruit Gerig.

USTAR is an innovative, aggressive and far-reaching effort to bolster Utah's economy with high-paying jobs, making Utah a vibrant participant in the Knowledge Age. To do so, it recruits world-class faculty members whose technologies can be commercialized. "The imaging technologies developed by Guido and his colleagues have very broad applications –from studying neurological disorders to studying atrial fibrillation



Brain growth between age 2 and 4 years visualized as colored brain surface. Dark blue indicates regions of largest growth as shown in the fore-brain and tips of the temporal lobes.

to visualization tools that provide insight into highly complex biological systems," points out Dinesh Patel, PhD, the chairman of USTAR's Governing Authority Board. "Each of these technologies target commercial markets that have potential to generate hundreds of millions in revenues."

Mapping Out the Next Five Years

It is an autumn evening, and in his office, Gerig looks out at the lights emanating from the University of Utah Medical Center, a block to the east. His door is still open, in case another student shows up; the janitors have just cleaned the white boards outside his office and pushed the beanbag chairs back into place.

His mind is on the recent five-year grant renewal for IBIS. Gerig's mind moves on to the next stage of IBIS; he wants to confirm the early findings and refine the imaging and the image processing by implementing more time points on the age spectrum, increasing their insight into short-term changes happening in an infant's brain. He wants to add a new component using fMRI technology to view connectivity changes over time; not just anatomical views, but real-time, 3-dimensional, functioning views of the brain.

He begins to imagine what the functional connectivity maps to display these changes could look like. No doubt, these images would exhibit colorful facts, visually capturing more clues to aid autism investigators, and further illuminating the possibilities for answers that may lie just beyond what we know today.

What is the Scientific Computing and Imaging (SCI) Institute?

"SCI offers an excellent computational infrastructure at a scale which allows us to pursue the computing necessary on large clinical studies," points out Professor Guido Gerig, PhD. "Further, the building and environment fosters and even invites collaboration among students, postdoc and faculty."

Since 1994, the SCI Institute at the University of Utah has established itself as an internationally recognized leader in visualization, scientific computing, and image analysis applied to a broad range of application domains. The overarching research objective is to conduct application-driven research in the creation of new scientific computing techniques, tools, and systems.

An important application focus of the Institute continues to be biomedicine. However, SCI Institute researchers also address challenging computational problems in a variety of application domains such as manufacturing, defense, and energy. The institute's research interests generally fall into different areas: scientific visualization, scientific computing and numerics, image processing and analysis, and scientific software environments. SCI Institute researchers also apply many of the above computational techniques within their own particular scientific and engineering sub-specialties, such as fluid dynamics, biomechanics, electrophysiology, bioelectric fields, parallel computing, inverse problems, and neuroimaging.

The SCI Institute either directs or is associated with several national research centers, including: the NIH Center for Integrative Biomedical Computing (CIBC), the DoE Visualization and Analytics Center for Enabling Technologies (VACET), the NIH National Alliance for Medical Image Computing (NA-MIC), the DoE Scientific Data Management Center, the NIH Center for Computational Biology, and the DoE Center for the Simulation of Accidental Fires and Explosions (C-SAFE).

In July, 2008, the SCI Institute was chosen as one of three NVIDIA Centers of Excellence in the U.S. (University of Illinois and Harvard University are the other two NVIDIA Centers).

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