

Genome LIFE



Bias on the Brain

Brain Studies Seek the Genetic Roots of Our Differences in Personality and Behavior

Are you someone who revels in the thrill of a roller coaster ride, or do you find yourself cringing at the mere thought of all those twists and turns? Do you obsess over problems and criticisms, or do you step back and consider the bigger picture? Your answers to these questions, along with the many other ways in which you react and respond to events in your life can ultimately be traced back to crackles of activity in your brain. Duke's Ahmad Hariri wants to understand those brain patterns, where they come from, and ultimately how they make each of us who we are.

"I'm fascinated by how incredibly different people are from each other, not just in the way they look but in the way they respond behaviorally to their worlds, to each other, to the challenges they face and the stress they encounter," says Hariri, professor of Psychology & Neuroscience and member of the IGSP. "That's what drives us."

In an effort to sort all that out, Hariri has embarked on an ambitious effort he calls the Duke Neurogenetics Study. Billed as the largest study of its kind in the world, the effort is designed to establish a database of overlapping behavioral, neural and genetic measures, allowing both exploratory genome-wide studies as well as more careful consideration of the role obvious gene candidates play in defining our personalities and our behaviors. Ultimately, the goal is to trace those differences back to their tangled roots.

Duke students enrolled in the study visit the Hariri lab three times to undergo IQ and memory testing, take a mental health screen, and answer more than 600 questions about themselves. Each participant's brain is then scanned by magnetic resonance imaging (MRI) to assess brain function and how different parts of the brain are connected to one another. Finally, students offer up a saliva sample that is then sent off to personal genomics company and research collaborator 23andMe for genome analysis.

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Bias on the Brain (continued)

Fear Factors

Hariri says they have almost 350 undergraduates enrolled thus far, and they hope to reach 500 by this spring semester. Ultimately, they aim to build the database up to 1,000 individuals. “We need a database at least that large to look at gene-gene interactions, gene-environment interactions, and moderators of pathways,” he says.

Most of Hariri’s work to-date has focused on what he refers to as the low-hanging fruit. That includes gene variants in pathways already known to influence brain chemistry: the neurotransmitters serotonin and dopamine, for instance.

In the mid-1990’s, other studies had linked variation in the expression of a serotonin transporter gene to differences in neuroticism and anxiety. Serotonin was also known to influence normal fear.

Hariri was able to show that people with one or two copies of a particular version of serotonin transporter associated with higher serotonin activity had a more active amygdala, the brain’s central processor of fear. He later found that variation in genes related to the neurotransmission of dopamine influence impulsive behavior through their effects on reward centers of the brain.

None of this is to suggest that a person’s genes alone can tell you much about how that person will behave in the real world. A report from Hariri’s lab earlier this year showed that perceived social support can act as a kind of buffer for our genetic predispositions. While the genes we carry may influence the way our amygdala lights up in response to threats, the anxiety we experience depends on whether or not we feel supported by those around us.

“Genes provide the starting point, and that’s it,” Hariri says. “They affect some small bias in the way the brain of an individual processes information.”

Game of Life

That bias in the brain isn’t necessarily good or bad, he says. One version of the serotonin transporter can mean a predisposition toward anxiety and depression. But it can also mean a more sensitive, open and compassionate person. Likewise, a different variant can be associated with a lower risk for anxiety, but also a callous lack of emotion.

The way that differences in amygdala activity play out in the world depends on the activity in still other parts of our brains, including those that regulate our

behaviors. Sorting all that out will take a very large sample size, Hariri knows, and that’s exactly what he is after with his neurogenetics study.

Hariri’s approach has been described as a creative blend of the latest neuroimaging techniques, genomics and good old-fashioned personality tests. While Duke colleagues Avshalom Caspi and Terrie Moffitt have relied on longitudinal studies to discover, for example, that the serotonin transporter gene is linked to risk for long-term mood disorders only in those who have also experienced trauma (see “Life Courses” in the September/October 2011 issue of *GenomeLIFE*), Hariri promises to find the biological underpinnings in the brain that help to explain those findings.

“Ahmad has sort of single-handedly launched this new area that he calls imaging genetics,” Moffitt has said. “Mastering either imaging or genetics is quite enough to ask of a young scientist, but he has somehow managed to master both of them.”

Hariri says his imaging genetics approach holds special promise because patterns of brain activity offer a reasonable approximation for the underlying brain chemistry, which is otherwise very difficult if not impossible to measure. His group is also beginning to come up with ways to combine genes that are related to particular brain signals and consider them jointly. His team recently showed they could account for about 10 percent of the variation in reward-related activity in the brain based on a five-gene profile.

Still, there is a long way to go and Hariri likes to joke that the complexity of the task will ensure his own job security. “We’re not going to stumble on any definitive answers in the foreseeable future,” he says. “We’ll just keep plugging away at it.”

The magnitude of the challenge has only grown with the realization in recent years that none of this is fixed; it is more aptly described as a dynamic interplay.

“Our genes are at the “GO” square on the Monopoly board of life,” Hariri says. “They set the stage for brain chemistry and circuitry, but they are also reshaped as their expression is modified by our experiences. It’s a constant back and forth, and it all comes back to what is happening inside our brains.”

Clinical Indications

Although Hariri got his start in imaging genetics as a postdoctoral researcher in a lab largely focused on schizophrenia, he is clear that his main interests as a biologist and neuroscientist by training aren’t in mental health or disease. That’s why his study focuses on healthy undergraduates as opposed to people representing this or that diagnosis. Nevertheless, the work he does is likely to yield new insights into mental health and psychopathology that will prove clinically useful.

For one thing, a better understanding of the brain pathways underlying behavior could lead to better drugs, he says, noting that the familiar SSRIs (selective serotonin reuptake inhibitors, including Prozac and Paxil) are effective in less than 50 percent of the people who take them.

“Targeting serotonin for depression is not at all dissimilar from using aspirin for a headache,” he says, citing a commonly used analogy. In neither case is

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—Ahmad Hariri

there compelling evidence that the drug acts on the source of the problem.

Methods used to profile brain activity and chemistry, perhaps using genomic scans as a proxy, might also help to determine the best course for therapy. Some people surely do need drugs to stabilize them before they can learn strategies to better cope with their emotions. Others might be able to skip the drugs completely.

In some cases, it may even be possible to avert mental illness altogether, by acting on pathways in the brain early. "That's the dream," Hariri says. His work suggests that this might sometimes be as simple as instituting programs ensuring adequate social support, especially for young people whose brains are less mature and less able to regulate themselves.

Under Your Skin

Even though participants in his study do get free access to their 23andMe results and he has had his own genome scanned, Hariri cautions that genome testing for behavior or mental illness is not in the cards now.

"In terms of its general value for predicting one's risk for mental illness or general behavior, it's no better than having your palms read at this point in

time," he says, while noting that some genetic information provided by 23andMe is already useful in helping individuals understand their relative risk for other types of diseases such as cancer.

He is nonetheless supportive of such services making the information available to those who want it and is convinced that 23andMe's consumer service will ultimately help to move the science forward. Without their assistance as research collaborators, Hariri would be unable to get the genomic data that his neurogenetics study depends on.

"I was amongst the doubters of 23andMe and other direct-to-consumer companies," Hariri admits. "I went to the initial meeting not wanting to collaborate, but left with a different perception of what they are doing and of what we can accomplish together. They need scientists to work with them, to help shape and restrain the findings that are reported back to consumers, and to move forward."

Ultimately, Hariri says the biggest misconception out there when it comes to individual differences is that "they're only skin deep. Differences in our behavior are as great, if not greater, than those in our physical appearance. More importantly, these individual differences often predict who might succumb to stress and hardship and who will be resilient." ▶



Ahmad Hariri's Duke Neurogenetics Study aims to explore the roots of our differences in personality and behavior through a combination of genetic and brain imaging studies.

An App for That?

Developing a Practical Genomic Test for Radiation Exposure

In the wake of September 11, 2001, the federal government committed billions of dollars to protect Americans from another attack – particularly one using weapons of mass destruction. The funding has gone into more than military operations; it has also driven scientific research aimed at developing new tests and treatments for use at future Ground Zeroes. Among the first researchers to enlist in this new offensive against potential terrorism were John Chute and his Duke colleagues, who have been developing a genome-based method to rapidly measure radiation exposure in the event of a nuclear event or “dirty bomb.”

“If a dirty bomb or an improvised nuclear device were to be used in a terrorist attack today, tens-to-hundreds of thousands of people could be exposed and an equal number petrified that they had been exposed,” said Chute, an associate professor of medicine and IGSP member. “We would need a way to triage those who had minimal or no exposure and needed no treatment, those who were lethally exposed and required comfort care, and those who had a level of exposure that could benefit from treatment. None of the current tests fits that bill.”

With funding from the Biomedical Advanced Research and Development Authority (BARDA), Chute and his collaborators are on course to correct that rather dismal state of affairs.

Basic Training

Chute seems a likely character to command such a mission, considering that he has spent much of his career in service to his country. He attended Georgetown University Medical School on a Navy scholarship, which he later paid back as a resident and attending physician at the National Naval Medical Center in Bethesda, Maryland. It was then that Chute began his own research at the Navy Medical Research Institute – an entity with a long history of research focused on the effects of radiologic or nuclear exposure on the troops. When he came to Duke in 2004, Chute was eager to expand his studies on the effects of radiation on the blood system, this time focusing on the genomic response to radiation exposure.

Scientists already knew that high doses of ionizing radiation could wreak havoc on the blood and immune systems, leaving the body vulnerable to infections and bleeding and increasing the risk of cancer. But these symptoms don’t show up until days to weeks after exposure, when it’s too late for treatments aimed at building back the body’s defenses. Methods available for measuring radiation injury – cytogenetics to look at damage to the cell’s 46 chromosomes or lymphocyte studies to count immune cells as they die off – simply take too much time in the event of a mass casualty.

“Changes in gene activity in the circulating blood can be an excellent sensor of exposure to injuries not visible to the human eye.”

—John Chute

So Chute joined forces at Duke with Nelson Chao, RadCCORE (Radiation Countermeasures Centers of Excellence) principal investigator, and the IGSP’s Holly Dressman and Joe Nevins to create a test based on gene chips to assess the body’s response to radiation at an even more fundamental level.

Dressman, Director of the IGSP’s DNA Microarray Core Facility, led an effort to subject mice to different doses of radiation and look for the impact of each dose on specific genes in the blood. That work showed that each radiation dose produced distinct gene patterns, which could be used to predict the degree of exposure. The researchers then repeated the same experiment in blood samples from human patients who had been treated with high doses of radiation, finding that a gene expression profile in human peripheral blood could be applied to predict the radiation status of people with high accuracy.

The researchers recognized that a number of variables – sex differences, genetic makeup, and time since exposure – might affect the precision of the test once they moved it out of the laboratory and into the real world. In a follow up study, Chute’s team showed that the test remained accurate, no matter what they threw at it.

Consistency Counts

The Duke team has now taken that laboratory test into the next stage of development with the aid of their BARDA funding, which could eventually reach more than \$43 million. At the end of that time, Chute says they hope to have created a portable instrument that can screen thousands of samples – based on just a droplet of blood per person – in less than an hour.



To reach that goal, the Duke team essentially went back to the drawing board. They've teamed up with IGSP Computational Biologist Joe Lucas to identify those genes that consistently respond to radiation in the same way in mice, human blood samples and in patients exposed to radiation in the course of treatment for other medical conditions.

"We've got pretty compelling evidence now that our test should do what it is supposed to do," Lucas says. He has been able to build predictors using the mouse and blood sample data that work in identifying radiation exposure in the human patients. The next step is to apply those predictors to non-human primates.

Lucas says that if the genes identified in mice and humans work in primates, there is every reason to think they would also work in an everyday group of healthy people after an accidental exposure, such as the one following the earthquake in Japan earlier this year, or an attack.

The Duke team will send that carefully selected list to a company called DxTerity Diagnostics, which has developed a proprietary technology that can essentially do the same work as a gene chip but in a more focused and less costly manner. The goal is to find those genes that translate well from one platform to the other.

"We want to use a drop of blood from a finger prick to look at a handful of genes, not thousands, and place people in bin A, B or C," Dressman says. Chute says it now appears that as few as 15 genes might do the trick as far as a week out after exposure.

In August, BARDA recognized the project's success with a grant renewal of \$10.8 million. The Duke researchers are the only BARDA awardees to have reached this phase of the award and secured further funding. They plan to use the money over the coming year to develop the prototype assay and instrument with the end goal of government procurement in two years.

Chute's team is also partnering with colleagues at the University of Arizona, an institution with a proven track record of turning homegrown academic center assays into practical diagnostics. For example, Frederic Zenhausern and his colleagues developed MiDAS, a desktop-printer sized instru-

ment that the FBI now uses at crime scenes for rapid turnaround DNA fingerprinting. Chute envisions a similar instrument for his radiation assay.

Once a device is ready, Chute and his colleagues will help to verify its accuracy by gathering and testing as many as a thousand human samples from patients at Duke, as well as Dana Farber and Memorial Sloan Kettering, who have undergone radiation treatment in preparation for bone marrow transplant.

The Next Defense

If all goes as planned, that collaboration could lead to a critical first line of defense in the event of a nuclear attack, by creating a way to quickly and easily screen tens of thousands of people for radiation exposure. That would be a major coup, but RadCCORE Director Chao and others won't be satisfied until they have a more comprehensive arsenal against the damaging effects of radiation.

"We are interested in studying the specific genes that came up in this genomic test," Chao said. "We hope that by understanding the cellular pathways that are affected in response to radiation – such as oxidative stress or DNA repair – we may be able to figure out ways to block or enhance these pathways as therapies."

Their team has identified a number of commonly used drugs that target the genes implicated in radiation response. Now they are screening those compounds to see which ones actually protect against radiation injury. Chute is quick to say that it is this glimpse into the biological underpinnings of the body's response to radiation that excites him the most, especially given its treatment implications.

"At the end of the day, even if we are able to develop a wonderful test for radiation that can allow us to triage people based on their radiation exposure, we still have a substantial need to develop therapies for those people who need them most," said Chute. "That is on our minds in all of the research studies that we are doing – how we can use the biology to identify and develop novel therapies to mitigate radiation injury – because that is the bottom line." ▶



Follow the Lead

Beyond radiation exposure, scientists at Duke are using gene chips to assess a number of manmade and environmental exposures as well. It's a method that has been applied to everything from cancer to viruses, and Chute believes the techniques could be useful for just about any public health concern.

"Changes in gene activity in the circulating blood can be an excellent sensor of exposure to injuries not visible to the human eye," said Chute.

Most recently, he and his team have used their approach to uncover genomic responses to lead exposure, one of the most common and preventable poisonings of childhood.

Chute and his fellow researchers reported in August that many genes do respond sensitively to lead exposure. What's more, their blood based signatures detect exposures at a level well below that set by the Centers for Disease Control and Prevention, offering the potential for better monitoring and tracking of health risks.

Further Reading:

LaReche HG, Meadows SK, Nevins JR, Chute JP (2011) *Peripheral Blood Signatures of Lead Exposure*. PLoS ONE 6(8): e23043. doi:10.1371/journal.pone.0023043

Peril and Progress

Allen Rodrigo on NESCent, Interdisciplinarity and the Challenges of Modern Biology

Allen Rodrigo's research interests can be described as anything but narrow. In the last year alone, his name turns up on publications on topics ranging from the complex microbiota of marine sponges to the antiviral activity in HIV-infected patients.

As a computational biologist by training, that diversity of interests is quite fitting for Rodrigo, Professor of Biology and Director of the National Evolutionary Synthesis Center (NESCent). NESCent's mission is to promote the synthesis of information, concepts and knowledge to address significant, emerging or novel questions in evolutionary science and its applications.

NESCent, a collaboration of investigators from Duke, UNC and NC State, encourages researchers to make greater use of existing data and to think about problems in new ways. All those data hold vast potential, but Rodrigo also sees that there are perils, as he and his colleagues wrote in an article entitled "The Perils of Plenty: What are We Going to Do With All These Genes?"

"The seductive appeal of large amounts of data seems to rest on a relatively contemporary belief that biological understanding emerges only when we have a handle on the componentry and mechanics of the organisms we study," they wrote. "And yet, if the last 200 years has taught us anything, it is that much insight emerges when we view the world at a sufficiently high level. Evolution, Mendelian genetics and the structure of DNA – the foundations on which modern biological science are built – emerged without the luxury of the vast quantities of data we now have. Consequently, we believe that the firmest challenge for twenty-first century biology is to work out what information we need to keep, what we need to ignore and how to summarize effectively and appropriately."

Rodrigo, who is also a member of the IGSP, spoke with *GenomeLIFE* about those modern-day scientific challenges, his experiences at NESCent, the nature of collaboration, and his own work.

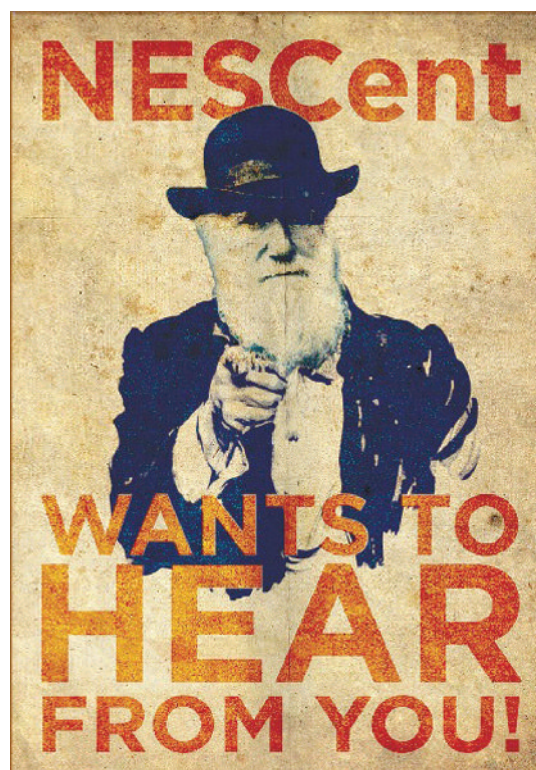
GenomeLIFE: First of all, NESCent strikes me as a pretty unique place. In a nutshell, what is it all about?

NESCent is one of a handful of NSF-funded synthesis centers. The idea behind these centers is this: there are a lot of data out there and not enough work to integrate or come up with new ways of analyzing that data. Our center doesn't generate anything new in terms of data; rather we try to better utilize and reuse data that are already available. NESCent has since broadened that concept even further. It is not just synthesis of data, but also of concepts, methods, disciplines and perspectives. It is that level of interdisciplinarity that characterizes NESCent.

NESCent is also a place where scientists can come and meet in working groups to focus on scientific questions and also where they can find the informatics infrastructure needed to develop tools and databases. It's a science incubator where ideas and research that are not quite ready for funding can come to develop.

GenomeLIFE: Can you give me an example of how NESCent engages in new ways of thinking about biological data?

To give you an idea, I spent the last three days at a meeting on evolution, astrobiology and synthetic biology. There were about 30 participants there from a wide range of disciplines and one of the things discussed was whether there are laws of biology. This becomes important because if you can identify laws of biology, then you know how to look for new life. It also tells you how to design a living system. There is also the idea that genetic systems can be characterized as logical systems with a grammar of their own and can be analyzed using tools of logic. If left to their own devices, astrobiologists are unlikely to speak to philosophers or computational biologists. Just bringing people together in the way that NESCent and the IGSP does can be remarkably productive.



Led by Allen Rodrigo, NESCent supports and catalyzes interdisciplinary research aimed to synthesize evolutionary data, methods and concepts.

“When does 'statistically significant' become 'biologically significant'? This is an issue I feel is important for modern genomics. We need to start thinking more smartly about how we collect and analyze our data.”

—Allen Rodrigo

GenomeLIFE: When most people think about evolution, they probably think about understanding the diversity of life and the relationships among species. Do you think about evolution as a field in a broader sense?

That's a great question. Over the last ten or twenty years, there has been a growing realization that you can take evolutionary principles and apply them in other areas. The idea that evolutionary principles are broader than just biological organisms is something that we get very excited about at NESCent. We are currently supporting a group that is working on the evolution of languages and another studying how evolutionary principles can be brought to bear on economics. We've just made a call to support evolution and social sciences. There are other areas where I think evolution could make more headway. Evolutionary medicine has been around for a long while, yet it hasn't permeated the minds of clinicians or biomedical researchers to extent that it could. Evolutionary medicine is broadly the idea that the consequences of human evolutionary history play out day to day in human health. At least some of this is due to a mismatch between the way we are in terms of our biology and the way we live.

If you ask a clinician about evolutionary medicine, most likely they will ask, "How am I going to use this?" It's an interesting struggle. Should we think about evolutionary medicine from the perspective of application only, or is it sufficient to say that if we can understand the causes – why things are the way they are – then that is a good thing in and of itself?

GenomeLIFE: As genome technologies have gotten cheaper and faster, there is clearly an acceleration in the amount of data that's available. Does that present any really new problems, or is it just a matter of scale?

The thing that worries me most about the way genomics is done in many cases is that it's essentially a shotgun approach. We take a community and sequence the heck out of it, then ask, now what can we discern? Erin McKenney, a graduate student working with Anne Yoder and me, is studying the metagenomics of the gut microbiome in lemurs, and the tack she's taking is one of hypothesis-driven genomics. Let's think about what we can expect to find in

these communities and make some hypotheses that are reasonable. Then we'll do the sequencing, and analyze the data to test these hypotheses. It's a structured approach that stops you from falling in the trap of seeing patterns that emerge just because people are good at seeing patterns. One of my problems is that everyone sees patterns all the time and some of these might even be statistically significant. But there are broader issues. How many patterns did I look for, and how many could have fooled me into thinking that something real is happening? In other words, when does "statistically significant" become "biologically significant"? This is an issue I feel is important for modern genomics. We need to start thinking more smartly about how we collect and analyze our data.

GenomeLIFE: But isn't this part of taking an "unbiased approach," meaning that you aren't limiting yourself to finding only what you expected to see?

To me, that seems diametrically opposed to the kind of hypothesis testing we should be doing. Imagine if you begin with a rational hypothesis based on what the biology leads you to think may be happening, and suppose you find something different from what you expected. How cool would that be? Because then, all of sudden I've falsified a hypothesis. It tells me that something that went in to making that hypothesis – some assumption, some "fact," some previous theory – was wrong. The biology is suddenly exciting! Otherwise, we'll find some genes – then what? Now, it's different if you are using an experiment to generate hypotheses. But at some point, it seems to me you have to formulate hypotheses. Otherwise there is no commitment and the science doesn't progress.

GenomeLIFE: What other lessons from your experience at NESCent do you think might be particularly relevant to us at the IGSP?

We at NESCent recognize the value of interdisciplinarity, and the IGSP is another prime example of that. Our communities are distinct yet overlapping, and I think the philosophies are to a large extent the same. Success in interdisciplinary research requires that you establish a common language and common priorities because the way one person perceives the problem at hand might be different from the way another person perceives it. I think the best way to do this isn't by holding seminars, but by getting people sitting around a table and talking about these things. ▶



Rodrigo is Director of NESCent and a Professor of Biology at Duke. Prior to his arrival at NESCent and Duke, he was a Professor of Computational Biology and Bioinformatics at the University of Auckland in his home country of New Zealand. He has been elected as a Fellow of the Royal Society of New Zealand and has received numerous honors for his research and teaching.



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IGSP Events & Opportunities

The IGSP invites proposals for funding innovative activities that advance its interdisciplinary mission across the Duke campus. Proposals that expand participation of the Duke faculty in the study of the genome sciences and policy and that catalyze new interactions across campus are particularly encouraged.

Details at

genome.duke.edu/about/funding-opportunities

Don't miss out! The IGSP offers and supports an array of regular and special events in Genomic & Personalized Medicine, Science & Society, Systems Biology, Computational Biology, Education and more.

“One of the things that's not very widely understood is that science is the major cultural driver, certainly for the last few hundred years and possibly for thousands of years...Let us not forget how important it is to keep science free and open for that purpose alone.”

— **Sir John Sulston** *speaking at the inaugural James B. Wyngaarden Distinguished Lecture in Genome Sciences & Policy on November 14, 2011*

> **Details on funding, events, the latest news and much more at the all new genome.duke.edu**

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