



Mining Genes, Data and Human Brains to Assess Mood Disorder Risk

More than 100 years of research on familial bipolar disorder hasn't revealed much about its specific genetic causes. But all that's about to change, says psychiatric epidemiologist **Peter Zandi**, thanks to advances in genome data analysis and sequencing—and access to human brain samples to tease out clues.

Since 2016, Zandi and psychiatry researcher **Fernando Goes** have partnered with **Thomas Hyde**, chief medical officer at The Lieber Institute for Brain Development, a Johns Hopkins University School of Medicine affiliate, and colleagues to study brains from people who struggled with mental illness and have passed away. The team aims to identify genetic risk for bipolar and major depressive disorders.

“Our goal,” says Goes, “is to find etiologic clues that will ultimately lead to new, urgently needed, targeted drugs.”

Located on the East Baltimore campus, the Lieber Institute houses the largest collection of donated human brains in the world for the study of psychiatric disorders (see sidebar). Researchers there are also using advanced technology to sequence genetic data and translate new insights into clinical advances.

The Lieber partnership builds on previous work by Goes et al., published in June of 2016 in *JAMA Psychiatry*. That study looked at eight

families with a history of bipolar disorder through several generations, suggesting a significant

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—FERNANDO GOES



inherited component. Ultimately, the investigators sequenced the whole genomes of 36 family members with the disease. Examining only the portion of the genome that acts as protein blueprints, they identified 84 rare gene variations that stood out in these family members.

Goes acknowledged that “it will take genetic data from at least several thousand more people with bipolar disorder to confirm that these rare mutations do in fact directly cause the disease.” Now, he and his research team are working on large-scale genetic studies with the Bipolar Sequencing Consortium to gather more data and

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Brain Repository Drives Research and Progress

In the eight years since the **Lieber Institute for Brain Development** was established, its leaders have tackled one of science's most vexing frontiers: psychiatric disorders. They believe the only way to make any real progress is to study actual human brains.

A Johns Hopkins affiliate, the institute houses more than 3,000 brains on the East Baltimore medical campus. According to Chief Medical Officer **Thomas Hyde**, this repository is considered the largest collection of postmortem human brains dedicated to the study of psychiatric disorders in the world. Most have been donated by families whose loved ones died unexpectedly. The collection fills nearly a dozen freezers set to minus 80 degrees Celsius.

Hyde's team of researchers apply a meticulous method to every case, examining each brain's defects while producing a thorough clinical characterization. They use lab techniques to isolate RNA, DNA and proteins from selected regions of the brain, before tapping into genetic technologies to better understand underlying neural mechanisms. Through big data applications, researchers are developing statistical models for large studies on gene expression.

These efforts, says Chief Executive Officer **Daniel Weinberger**, could identify novel biological pathways tied to schizophrenia and other serious brain disorders. Ultimately, the team of 106 researchers at the institute hopes to pinpoint how genetic variation influences brain development.

So far, more than 1,000 human cell lines have been generated; more than 500 from the brain samples (the first 500 came from the National Institutes of Health). Over 100 peer-reviewed papers have been published since the institute's founding. The institute has also leveraged more than \$45 million in grants and partnerships, while launching major clinical research ventures, including one with Peking University in Beijing. In addition, it has established what's considered the world's largest post-traumatic stress disorder (PTSD) human brain repository and has become a critical provider of tissue for the Department of Veterans Affairs for the study of PTSD.

Now, LIBD is pushing its genes-to-drugs pipeline strategy, having identified several new therapeutics. A few could be in clinical trials within the next three years, says Weinberger. Another four “promising leads,” he says, could produce two new drugs for Phase II clinical trials by 2021. The institute has also established Brain-SEQ Consortium, a precompetitive collaboration with seven leading pharma companies, as well as an open-access, cloud-based tool for genetic analysis of the human brain. “This public archive of human brain gene expression data,” says Hyde, “will enhance neuropsychiatric research at institutions around the world.”

Learn more about the Lieber Institute: libd.org





Jimmy Potash, M.D., M.P.H.

Groundbreaking Efforts, Empathetic Care

Welcome, friends, to the winter edition of *Hopkins Brain Wise*. Let me update you on **Roland Griffiths** and **Matt Johnson**, whose work on the hallucinogen psilocybin was featured in this publication last year. Both figure prominently in a fascinating book that was on bestseller lists for several months recently, Michael Pollan's *How to Change Your Mind*, which explores the science of psychedelic drugs. Pollan dates the modern era of psychedelic research to Professor Griffiths' groundbreaking 2006 paper. There are now two large-scale studies underway of psilocybin to treat depression. One of them just gained Breakthrough Therapy designation from the Food and Drug Administration (FDA), which represents significant interest from the FDA in helping to facilitate the development pathway for this drug. Another area we are pioneering is the use of virtual reality in behavioral therapy, as described in the Page 4 article on work by the very talented **Joe McGuire**. During my recent trip to the McGuire Lab, I donned goggles and was immersed in the astonishingly realistic virtual world the team creates, which opened my mind to the great potential of this approach to make a difference for young people suffering from anxiety.

This issue also features work from two of my close colleagues, **Peter Zandi** and **Fernando Goes**, both at the forefront of efforts to discover the causes of mood disorders. We are extremely fortunate to have the Lieber Institute for Brain Development, led by world-renowned psychiatric neuroscience researcher **Dan Weinberger**, here on our campus, as a generous partner in this work.

On the Johns Hopkins Bayview Medical Center campus, we have one of the nation's best community psychiatry programs, and you will read at right about a superb facet of it, the innovative Creative Alternatives, which serves the most severely and persistently mentally ill, not only directly treating their psychiatric disease, but also helping them with life skills and basic needs. I salute the tremendously dedicated staff there, who do whatever it takes to be responsive to patient needs.

Thanks to all of you for your interest in our work. My warmest wishes to you.

Mining Genes, Data and Human Brains to Assess Mood Disorder Risk (continued from cover page)



“Human DNA will set the stage to identify the mechanism and develop treatments that are much more effective than what we have now to turn those genes on and off.”

—PETER ZANDI

more collaborators “so we can definitely figure out causes.”

Zandi and Goes continue to use next-generation sequencing technology that allows them to churn through enormous amounts of DNA at a time. They're mining these data to uncover the role of rare variation—rare instances where the blueprint is faulty—in mood disorders.

As they made progress, says Goes, they were interested in how genes were expressed—turned on and off. Lieber, with its enormous brain collection and multidisciplinary expertise, was the preeminent place to turn. Goes leads a project focused on key brain regions likely to be involved in depression, and Zandi heads up a comparable project in bipolar disorder. Both studies look at how potential mood genes are regulated and how their functioning is altered.

“We really want to explain the specific mechanisms by which the genetic variants that have already been defined behave and how they contribute to risk for mood disorder,” says Zandi. “It's not just one variant in a gene; there are lots of variants across many genes that increase risk,” he says. “This collaboration will give us clues to those mechanisms.”

Zandi and his colleagues are hopeful that having complete information about the DNA from

each brain sample will offer deeper insight into how proteins are produced. “This could set the stage for developing new treatments that might influence those proteins and might include being able to turn those key genes on and off,” says Zandi.

Despite a wide variety of available medications for mood disorders, their overall effectiveness remains modest, says Goes. “It's one reason patients go off their medicines. And only a third of treated patients get fully better with them.”

The development of new types of antidepressants, he says, “has been hindered by our limited understanding of how exactly they work in a given patient.” Zandi and Goes envision a day when discoveries based on a person's risk for mood disorder will lead to treatments as targeted as immunotherapies are becoming for patients with cancer.

“Within the next several years, we expect to find very specific mechanisms. It's still tip-of-the-iceberg, but through this work, we will help lay the foundation for more rationally designed interventions.”

For now, the collaboration with Lieber, says Goes, is a vitally important step. “We hope it will be a game changer in preventing risk for developing mood disorders, which too often lead to suicide.” ■

COMMUNITY PSYCHIATRY



PHOTO: JON CHRISTOFERSEN

“It's about giving people meaningful roles,” says Creative Alternatives program manager Sheila Goldscheider.

Community Psychiatry Program Extends Help to the Neediest Patients

Charles Rockstroh says he had it all. Then major depression took over, rendering him homeless and unable to work. He lived with relatives until they could no longer house him.

“I went from ER to ER, just to have a place to stay,” Rockstroh says.

Then he learned about Creative Alternatives. For 25 years, clinicians at this community psychiatry program, funded by the state and administered by Johns Hopkins Bayview Medical Center in efforts to keep people with major mental illnesses out of psychiatric hospitals, have

worked tirelessly to provide mental health treatment and rehabilitative living skills to its members.

About two years ago, a program representative came to Rockstroh's father's apartment to meet him. Impressed that Creative Alternatives would pay his rent until he found a place, he enrolled, taking advantage of individual and cognitive behavior therapy services. Now he lives with a girlfriend and holds a steady job in merchandising at a Home Depot. “I feel better about myself,” he says.

“The beauty of this program is we're able to help people with their lives in so many ways

Therapy Group Offers ‘Mature Coping Skills’ to Patients with Borderline Personality Disorder

For years, mental health clinicians struggled to manage patients with borderline personality disorder. While such patients represent just 1 to 2 percent of the population, they make up nearly 20 percent of those receiving psychiatric care.

Now, in addition to offering individual dialectical behavior therapy (DBT) sessions for patients, the Community Psychiatry Program at Johns Hopkins Bayview Medical Center has launched an adult outpatient DBT Skills Training Group. DBT uses a form of talk therapy that focuses on giving patients the psychosocial skills needed to tolerate unpleasant emotions and bring themselves down from a crisis.



“Borderline personality disorder used to be considered a poor prognosis condition with a poor response to treatment.”

—FRANCIS MONDIMORE

The group, facilitated by social workers **Michael Van Wert** and **Maryam Elbalghiti-Williams**, meets for 90 minutes a week for 16 weeks and aims to teach patients skills in the areas of mindfulness, distress tolerance, emotion regulation and interpersonal effectiveness.

This approach differs dramatically from those of the past, says **Francis Mondimore**, director of Johns Hopkins’ Mood Disorders Clinic and section director of outpatient psychiatric services at Johns Hopkins Bayview. “Borderline personality disorder used to be considered a poor prognosis condition with a poor response to treatment,” he explains.

In fact, some clinicians dreaded having to care for these patients because they required so much treatment and, based on the nature of their illness, frequently switched practitioners, he says. Traditional psychotherapy to try to understand their problems and sources of conflicts failed, as patients so frequently became suicidal or developed other self-harming behaviors that always triggered a crisis to manage, adds Mondimore, co-author of *Borderline Personality Disorder: New Reasons for Hope*. “They basically lurched from one crisis to another without ever making any progress.”

That changed in the 1980s with the advent of DBT. Through DBT, patients can learn to manage strong emotions, urges and reactions independently, without having to call others for help.

Unlike traditional group therapy, during which patients share what happened to them that week, the approach at Hopkins Bayview is more of



a classroom situation, says Mondimore, where patients are taken through practice exercises and given diary cards and homework. “It’s a very active form of therapy,” he says, designed to supplement individual therapy sessions. Although the first class filled within two weeks of advertising, it is a rolling program, with opportunities for new patients to join every four weeks.

“The goal is to give patients more in the way of mature coping skills to deal with their emotions, so that their emotions don’t carry them into self-destructive behavior,” says Mondimore. “They will learn to self-soothe and ideally be less prone to acting out in a crisis.”

Therapists referring patients are asked to attend a monthly DBT team consultation meeting with the social workers to better coordinate care and learn more about DBT principles and skills. ■

For more information or to refer a patient: 410-550-0105

that can ultimately benefit their mental health problems,” says psychiatrist **David Neubauer**, who has been with the program for about 20 years. Beyond mental health services, staff coordinators help members find housing, receive benefits such as Social Security or medical assistance, return to work or school, and get to doctor’s appointments for co-occurring conditions. At a drop-in center on the Baltimore City’s east side, members participate in men’s or women’s support groups, take yoga classes, enroll in substance

abuse treatment and learn to develop wellness recovery action plans.

“What makes us so successful are the relationships that we build with the members,” says nurse and program manager **Sheila Goldscheider**. Beyond medical management, she says, “It’s about giving people meaningful roles,” and asking what their dreams were before becoming ill. Personal service coordinators dedicate their time to just 10 members each. The program also plans social outings such as a crab feast, fishing trips

and Orioles games. An annual banquet honors members for staying sober, maintaining good relationships with family, or working.

Members average less than one hospital day per patient per year, says Goldscheider. About 10 percent are employed, and 65 percent live independently.

“Creative Alternatives is the best,” adds member Adrian Smith. “Some people say, ‘I don’t know what I would do without it.’” ■



“The beauty of this program is we’re able to help people with their lives in so many ways that can ultimately benefit their mental health problem.”

—DAVID NEUBAUER

Bolstering Emotional Support



The Department of Psychiatry offers additional wraparound services for patients. As one option, it is employing “telepsychiatry” appointments for adults with major mental illness who receive psychiatric management at home or in community settings through the Costar Assertive Community Treatment program. If a nurse or case manager observes an urgent situation, such as a patient not taking his or her medication, they can quickly alert the person’s psychiatrist and arrange a videoconference appointment on an iPad. While psychiatrists see all patients at least once a month, this provides a supplemental option for pressing issues, says **Bernadette Cullen**, director of community psychiatry.

The division is also studying automated text messages to help prevent relapse in patients with schizophrenia. In a research project funded by the National Institute of Mental Health, 28 of 40 patients who were enrolled in a randomized controlled trial receive daily text messages alerting them to one of five early warning signs of relapse, in addition to inspirational quotes and reminders to take medications. While the trial is ongoing, most patients receiving the text messages are responding, Cullen says.

Could Virtual Reality Improve Treatments for Kids with Anxiety or OCD?

Joseph McGuire is determined to change status quo treatments for young people with anxiety and obsessive-compulsive disorder (OCD). “Even with the best treatments available to us,” says the Johns Hopkins clinical psychologist and researcher, “outcomes for adolescents with anxiety or OCD aren’t great. And, even those teens who exhibit significant improvement often still have lingering symptoms.”

McGuire is conducting a virtual reality (VR) study—one of only a handful of such studies—to understand how adolescents acquire and eliminate fear—key aspects underlying the emergence and treatment of anxiety and OCD. The VR technology is a head-mounted display that portrays realistic and interactive computer-generated environments.

To perform the study, McGuire will evaluate whether adolescents (with and without these psychiatric conditions) become afraid of abstract stimuli, such as colored lamps, in an immersive VR environment. The adolescents will then go through steps to eliminate learned fear—which parallels the cognitive-behavioral treatment process. After that, McGuire

will use immersive VR to place adolescents in a new virtual environment with the same abstract stimuli to investigate whether they experience a fear response.

If McGuire can identify which aspects of fear extinction are most challenging for adolescents with anxiety or OCD, he can devise strategies to spark associations that better inhibit fear across settings. This is important because fears related to anxiety and OCD are often experienced in one setting—for example, home or school—but are regularly treated in another context, such as a therapist’s office.

“If we can improve our understanding of how adolescents acquire and eliminate fear across settings, it would lead to better clinical outcomes,” McGuire explains. “Immersive VR provides an engaging opportunity to get kids involved in therapy and to help researchers study learning processes that apply in the real world. It seems like a natural fit for young people.”

The study is based on McGuire’s previous research on fear conditioning and extinction learning in adolescents with OCD. He expects the study to last for several years.



Visit bit.ly/mcguirestudy to read McGuire’s latest published paper on this approach to cognitive behavioral therapy for children and teens.

To refer patients for the study, please contact jfmcguire@jhmi.edu.

Hopkins *Brain Wise*

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