



DEPRESSION CENTER

HEINZ C. PRECHTER BIPOLAR RESEARCH FUND
UNIVERSITY OF MICHIGAN

PRECHTERFUND.ORG

2014

PRECHTER MILESTONES

FROM THE PRINCIPAL INVESTIGATOR

The Heinz C. Prechter Bipolar Research Fund at the University of Michigan is one of the many legacies of Heinz Prechter, a Michigan man who truly changed the world. His family, Wally, Paul, and Stephanie, carry on his legacy of creating a better world through the Fund. Hardly a day passes without a remembrance of Heinz. A study participant, a supporter, someone attending a clinic appointment tells us they met Heinz and they remember a moment with him.

*The flagship **Prechter Longitudinal Study of Bipolar Disorder** reflects the participation and contributions of thousands! Through the experiences volunteered by so many, we will gain greater knowledge and understanding to form the base for improved treatments.*

Though more than 1,000 individuals volunteered for the Longitudinal Study, we have not lost our focus on the individual. The illness patterns of individuals with bipolar disorder vary considerably. Some individuals have frequent recurrences of significant symptoms; others have minimal symptoms over time and little interference with personal, social or vocational life. Bipolar disorder is not one illness. We talk of BPI and BPII but there are undoubtedly many subtypes and variations of this disease; the more severe forms include suicide.

*For this reason and many others, predicting and preventing episodes in the bipolar individual is a priority. Our collaborators in the College of Engineering led by Emily Provost, Ph.D., have created ground-breaking **software for smart phones** to capture outgoing speech on the phones and upload to a central server to analyze the acoustic patterns of speech in order to predict impending mood changes.*

This project has captured attention nationwide and we have had several media interviews on this topic.

*We are also working on research at a cellular level. **Our stem-cell program** is the vanguard of biological research. Our studies in the labs of Sue O'Shea, Ph.D., are the first reports of a cell-based model of bipolar using cells derived from patients. The signaling mechanisms between nerve cells is abnormal but is normalized with lithium. This offers a model to study cell function, helping us to discover new molecules and create new medications based on this research.*

Participate and contribute to research — solutions reduce stigma.

Live well,



Melvin G McInnis, M.D., FRCPsych
Thomas B. and Nancy Upjohn Woodworth
Professor of Bipolar Disorder and Depression
Professor of Psychiatry
Principal Investigator,
Heinz C Prechter Bipolar Research Fund

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What does the Prechter logo mean?

The blue ribbon "P" is surrounded by a white circle. It represents the cycle of the illness. Always in search for balance and wellness in life, patients with bipolar disorder alternate between the poles of "mania" and "depression." The blue ribbon breaking through the circle signifies the Fund's goal to advance breakthrough medical research to develop cures for the illness.



Dear Friends:

Thank you, as always, for your faithful support of the Heinz C. Prechter Bipolar Research Fund!

This is a pivotal year for the Fund, as we embark on the task of a bold fundraising campaign to ensure its sustainability and bright future under the direction of Dr. Melvin McInnis and Research Manager Gloria Harrington. I'm excited to announce that, to ignite the pace of new knowledge and treatments for bipolar illness, all gifts are being matched,

dollar-for-dollar, by a generous donor, so there has never been a better time to make a donation to the Heinz C. Prechter Bipolar Research Fund. I hope you will share this news with others who

might be considering becoming donors, in order to inspire them into action. We are extremely pleased and excited that our first stem cell study results were announced to a nationwide audience on March 25! They show that nerve cells created from bipolar skin cells behave and respond to lithium differently, and that knowledge opens doors to potential new and customized treatments for patients.

I know the future of the Heinz C. Prechter Bipolar Research Fund is bright and promising and, thanks to all of your support, we are able to see the light at the end of the tunnel!

Most Sincerely,

Waltraud E. Prechter
Founder, Heinz C. Prechter Bipolar Research Fund

Become a **Victor** for Bipolar Disorder

Now's the time – a donor will match your gift!

The Heinz C. Prechter Bipolar Research Fund at the University of Michigan Depression Center represents the future of bipolar research. No other program has its clinical, genetic and biological depth. The studies launched via the Prechter Fund are laying the foundation to transform complex brain-behavior mysteries into hope for the millions who are afflicted. While we have made great progress, there is still much more to be done — and we need victors to join in our mission.

Perhaps you know someone who has been touched by bipolar disorder, or you are passionate about a making a

difference in the world. There has never been a better time to make a profound impact and become a victor for bipolar disorder.

To ignite the pace of new knowledge and treatments for bipolar illness, all gifts are being matched, dollar-for-dollar, by a generous donor. Go to prechterfund.org to make your gift today, or call 734-763-4932 to discuss other ways you can support this important work.



VICTORS FOR MICHIGAN

“I think that if you can — if you truly believe in something — you owe it to yourself to help, to give, and to make a difference. Because ultimately that is all you leave behind.” — Wally Prechter

Meet Our Team: Sebastian Zoellner



Data analysis examines bipolar in terms of nature vs. nurture

Bipolar runs in families, but the details of the “what” and “how” have eluded scientists for decades. The answers are in the individual, where biology, personal disposition, and life experience intersect to create the “who” of the individual.

Integrating the biology — genetic data — with information of personal adversity and daily stress elevates the “nature-nurture” discussions to the level of sophisticated computational analyses. That is the daily work of Sebastian Zoellner, Ph.D., Associate Professor of Biostatistics and Psychiatry. Zoellner has been with the Prechter team since 2005 and leads the statistical analyses of all the data. A graduate of the prestigious Max Planck Institute in Leipzig Germany, he began with a degree in mathematics and has contributed extensively to analytic strategies of genetic

sequence and the relationship between mutations and disease. Dr. Zoellner's academic appointment is shared with the Department of Biostatistics at the University of Michigan School of Public Health.

Zoellner embraces the challenges of “big data” with a computational powerhouse of Ph.D. students and computer processors.

“Working with the Heinz C. Prechter researchers is very rewarding because of the diversity of expertise from the laboratory bench to the clinics,” Zoellner says. “The robust and inclusive data collection strategy is unique in Bipolar research and will provide answers and, ultimately, solutions.”

PRECHTER LONGITUDINAL STUDY OF BIPOLAR DISORDER

“Big Data” making a big difference

Detailed and deep data on 1,040 individuals

The term “Big Data” has a lot of connotations. To some, it may conjure the appropriation of personal data by large corporations — but in truth, Big Data really just means the availability of large amounts of data, and there are many instances where having that data is a good thing. One such example is the Heinz C. Prechter Longitudinal Study of Bipolar.

The data used in this study come from multiple biological and clinical domains gathered over several years of assessments and observations from each of 1040 individual participants. The key word here is *participants*. This study never would have happened without them. These volunteers offered their personal data in the interest of this study and the new treatment strategies that we may be able to develop as a result. That's where big data makes a big difference — because the more data we have, the more accurate the study will be. From these generous individuals, we were able to generate literally hundreds of billions of data points.

The goal? Define the disorder at its core and determine the predictive markers that can be used to prevent episodes.

Our methods:

- Participants are evaluated every two months.
- Participants completed regular questionnaires,

neuropsychological testing and clinical interviews coupled with biological samples (DNA).

- We acquired several additional big data sets in sleep, nutrition, physiology, and genetics.
- We are conducting extensive ongoing collaborations with 10 departments throughout U of M.
- We have created a national and global reach with academic non-profit partners as well as engagement with industry partners for clinical, genetic, and biomarker trials.

We're already putting the data to use in programs like these:

- Using stem cell technologies to study molecular models in nerve cells made stem cells of our bipolar participants.
- Using computational technologies to analyze acoustic patterns of speech gathered from cell phones in the field.

All of this has placed the Heinz C. Prechter Bipolar Genetics Repository on the vanguard of cell biology and technology based research in psychiatry, and all of our efforts align with the vision of the Prechter Fund and serve its mission.

We thank our partners in research, our supporters and donors as well as our study volunteers who participate and contribute at a very personal level.

Prechter
Bipolar
Repository
defines
“Big Data”

OVER

1000

Participants enrolled in the Longitudinal Study

Stem Cells – the Vanguard of Biomedical Research in Bipolar Disorder

Prechter scientists publish a stem cell model of BP

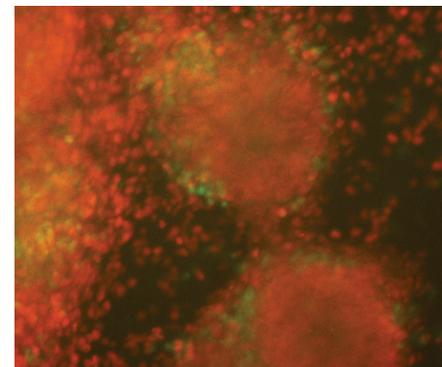
New stem cell research on bipolar disorder, conducted by the University of Michigan Medical School and the Heinz C. Prechter Bipolar Research Fund, is uncovering molecular mechanisms of this disabling illness.

In the March 25 issue of *Translational Psychiatry*, a team of researchers led by Sue O'Shea and Melvin McInnis published the report of the first stem cell lines generated from patients with bipolar disorder. When the scientists prompted the stem cells to become neurons, they found significant differences in signaling and development in brain cells from patients compared to healthy controls.

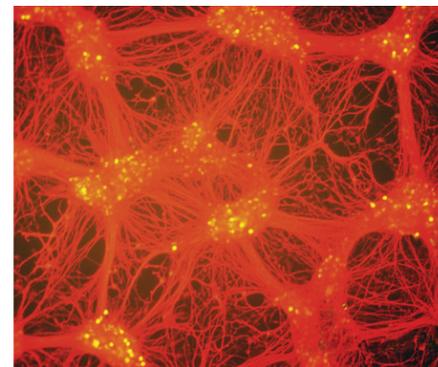
"This is an important and exciting study," said Chris Ross, Director of the Molecular Neurobiology Laboratory at the Johns Hopkins University, who was not involved in the study. "This work will help us better understand the disease and more importantly, develop new treatments for the more than six million Americans with bipolar disorder."

The Potential of Stem Cells

It starts with a skin biopsy the size of a pencil eraser. These cells are grown with pluripotency factors (a combination of genes) that induce them to become immature (*pluripotent*) cells — *stem cells*. The stem cells can then be coaxed into growing into any cell



NEURONS derived from a patient with BP. They were treated with lithium during their differentiation and stained to identify the specific neuronal subtype. Green cells will form excitatory pyramidal neurons and red cells will form inhibitory interneurons of the brain.



NEURONS from BP stem cells extend long processes to interact with each other. The red color identifies a structural protein in the axon (process) of the cells and the white color is present in nuclei of dividing cells.

type, including nerve cells. The nerve cells carry the basic genetic information of the person who was sampled. The brilliance of the approach is that it provides access to cells that behave like brain cells from a person with bipolar disorder. This cell model of bipolar allows scientists to study the effects of medications, stress, and other variables on the function of the brain cells.

Calcium Connections

Calcium is simple molecule, but it's widely involved in living cells. Nerve cells from people with bipolar have different receptors and channels related to calcium signaling — a key aspect of nerve development and signaling. Independent genetic research has implicated calcium channels as contributors to the disease. Lithium, a medication often very effective in the management of bipolar disorder, appeared to normalize the signaling process among patients.

"Signals between nerve cells are fundamental to brain functioning," McInnis points out. "A model for brain functioning opens the door for developing and testing novel treatments."

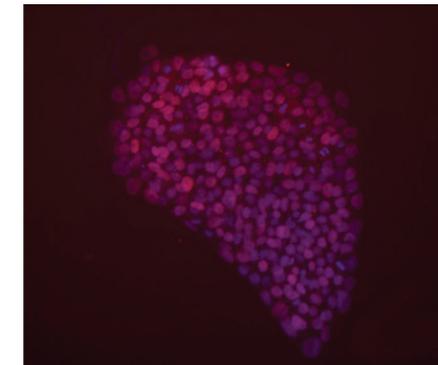
Developmental Diversions

Although the symptoms of bipolar disorder typically emerge in late adolescence or early adulthood, the underlying brain abnormalities seem to be present much earlier. In the current study, O'Shea, McInnis and colleagues found evidence that developing cells from

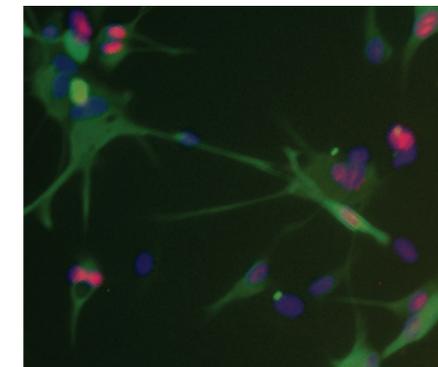
bipolar patients had differences akin to a transposition of a ZIP code that alters the destination of the cell. Are individuals with bipolar disorder "wired differently". Potentially.

The findings from these studies have implications beyond bipolar disorder. "This is a very promising demonstration of the potential value of cellular models of brain diseases," says Roy Perlis, M.D., Ph.D., Medical Director of the Bipolar Clinic and Research program at Harvard. "It's a technology that will change how we study these diseases, and while we still have a lot to learn, this paper provides a glimmer of what may be ahead."

What lies ahead is an expansion of the current study. More cell lines are under development, the team is expanding and collaborations established to replicate findings and establish the best bipolar model possible.



STEM CELLS from a patient with BP express the pluripotency factor *nanog* (red) and have been stained to identify nuclei (blue).



ASTROCYTES are the supporting cells of the brain. Here astrocytes from BP stem cells were stained with a green marker to identify a structural protein and with a blue dye to identify their nuclei. The pink regions indicate dividing cells.

8th Annual Prechter Lecture Series

Monday, September 29, 2014 • 1-4 p.m.

University of Michigan Depression Center Auditorium
Rachel Upjohn Building | 4250 Plymouth Road | Ann Arbor, MI 48109

Keynote Speaker:

Kathleen Ries Merikangas, Ph.D.

Senior Investigator and Chief of the Genetic Epidemiology Branch in the Intramural Research Program at the National Institute of Mental Health (NIMH)

Achievements:

Dr. Merikangas has authored more than 300 scientific publications and has presented lectures throughout the U.S. and in more than 20 countries. Her work has contributed to both methodology in epidemiology and genetics, including methods for studying causes of comorbidity and the development of the genome-wide association study approach to detect genes for complex diseases, and to substantive knowledge about comorbidity of mood disorders with substance use disorders in general population samples. Dr. Merikangas has also devoted substantial effort to training activities including mentorship of individuals and directing formal training programs in genetic epidemiology at both Yale and at the National Institutes of Health (NIH).

How Dr. Merikangas Is Helping:

Dr. Merikangas' research in the Intramural Program at the NIMH focuses on two major areas:

1. Population-based studies of mental and physical disorders including the first study of mental disorders in a nationally representative sample of youth in the U.S. and multigenerational family studies designed to identify the core features and biomarkers of genetic and environmental factors underlying the familial transmission of bipolar spectrum disorders
2. Co-transmission of mood and anxiety disorders with cardiovascular disorders and migraine.

Please join us. The entire program is free and open to the public. Please register at prechterfund.org/lecture.

In a study reported in the March 25 issue of *Translational Psychiatry*, a team of researchers led by K. Sue O'Shea and Melvin McInnis created the first stem cell lines generated from patients with bipolar disorder.

The Prechter Lecture Series is supported through the generosity of the following sponsors: Comerica Bank; Dearborn Sausage Company, Inc.; Fritz Enterprises, Inc.; Holbrook's Roofing Co., Inc.; and Scott Snow Financial Advisors, LLC

Living with Bipolar — a Fundamental Approach

It's common sense that diet and exercise relate to *physical* health. But can diet and exercise help manage bipolar illness?

"Good scientific studies indicate yes," says Simon Evans, Ph.D., coauthor of *BrainFit for Life*. "Studies show that a poor diet can increase the risk of major depression and that exercise can actually act as an antidepressant. Poor eating habits and sedentary behavior can cause weight gain and increase risk of heart disease and diabetes. What's less obvious is that they also relate to mental health." Visit choosemyplate.gov to find tips for eating healthy on any budget and achieving appropriated levels of physical activity for any age.

Sleep Matters Too

"Sleep is also a key factor," Evans adds. "We all know that we don't feel as well when we don't get enough sleep, but science also shows us that disrupted sleep can wreak havoc on our physical health as well, making us more likely to gain weight and even crave unhealthy sugary foods. For many, getting enough quality sleep is just a matter of prioritizing, but for others it's a real problem that would benefit with the aid of bringing a sleep professional into the treatment team."

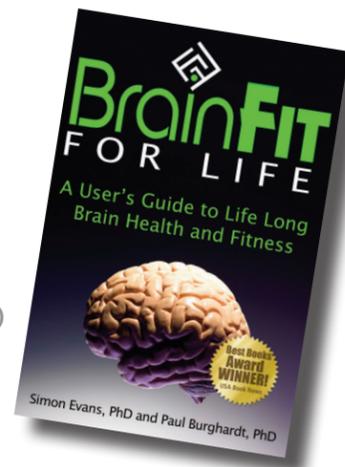


Simon Evans, Ph.D.

Stick to the Basics.

Evans points out that a focus on the fundamentals of health can lessen the burden of disease and potentially improve responses to medications or even reduce the need for medications. "The best part is that we all have a good deal of control over these fundamentals and we can choose to bring them to the forefront of any treatment plan," he adds. "It really doesn't have to be complicated. If you stick to basic advice, be skeptical of new health fads, keep your guilty pleasures in moderation, and stop looking for a shortcut, you'll do fine. I like to use the analogy of a sports car. Often times health care providers will be like mechanics, helping you tune up your body. In the case of mental health disorders, drugs may help tune your brain chemistry to run more smoothly. But if, when you drive away, you choose to put

sludge in your gas tank, the best tune up in the world will have limited value. The fundamentals of diet, exercise and sleep will help your health care provider help you much more effectively."



Simon Evans, Ph.D. is the co-author (with Paul Burghardt, Ph.D.) of *BrainFit for Life*, which can be found on amazon.com.

"Studies show that a poor diet can increase the risk of major depression and that exercise can actually act as an antidepressant." — Simon Evans, Ph.D.

The importance of listening: the PRIORI Project

"Doctor, I could hear it in her voice, and I knew the mania was around the corner."

We hear this frequently in the clinics and emergency rooms. Such observations by families and friends led investigators in the Prechter Longitudinal Bipolar Study to the hypothesis that the changes present in speech may be detected even earlier by computer analyses and used to anticipate and prevent an emerging manic or depressive episode. The PRIORI project is collaborative research between psychiatrists, social workers, and computer scientists to identify acoustic features of speech that associate with mood changes.

Prediction and prevention of bipolar episodes will intercept the consequences that change the lives of so many — including lost jobs, failed relationships, financial disasters and suicide.

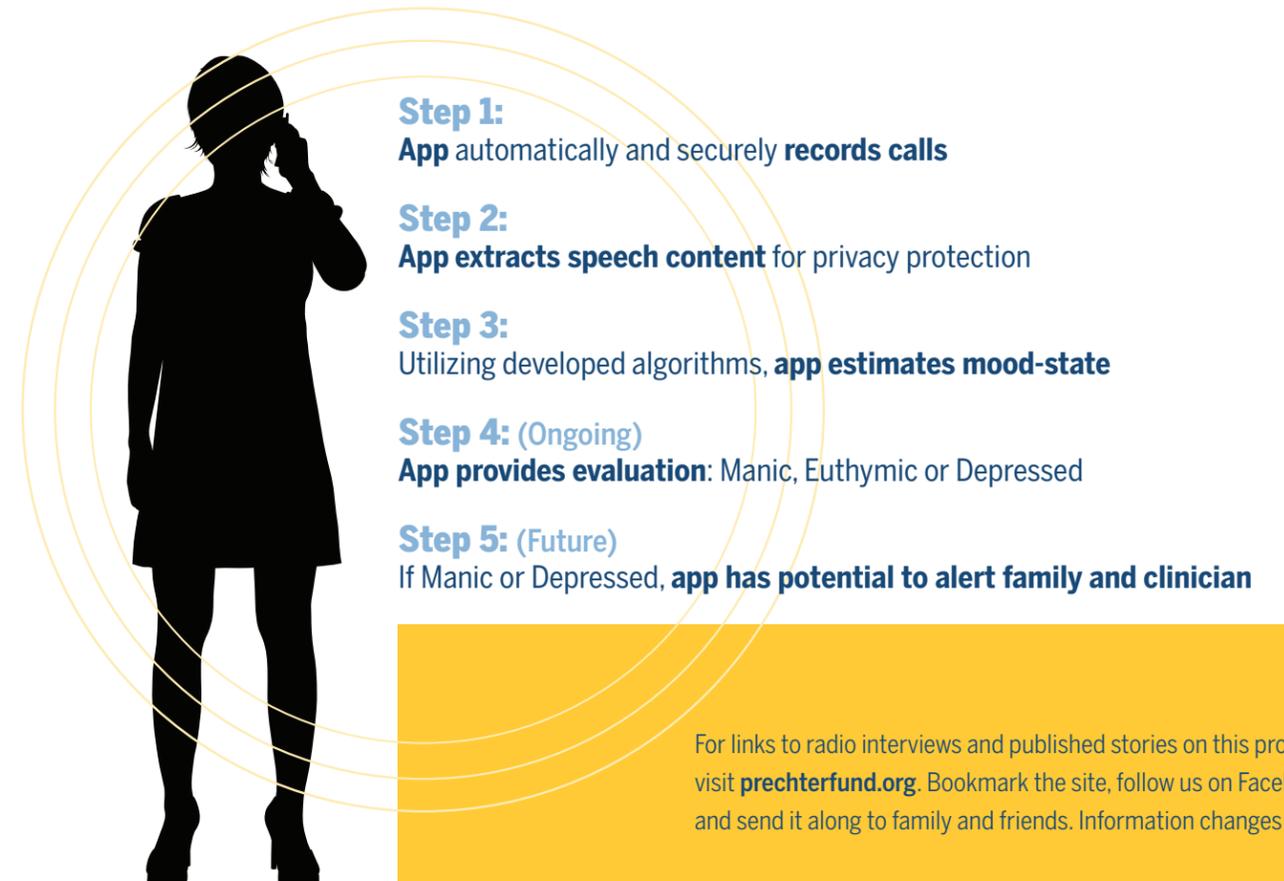
Why speech?

Speech is how we represent what is happening in our mind and emotions. And it's not just what we say, but how we say it. Listening involves paying attention to the tone and nature of what is being said. (Any parent of a college student will know the mood of their fledgling by listening to just one sentence on the phone, regardless of how well they say things are going.)

How it works:

PRIORI is novel and highly innovative. Rather than depending on the person filling out a mood rating or responding to a text, information is gathered over the course of daily activity — talking on the phone. The system runs seamlessly in the background on a device that has become an essential part of our daily lives, our smartphone. A new scientific term has evolved to describe how this data is gathered: ecological momentary assessment. It means gathering information at the moment in an ecological manner, integrating into the working environment of the individual. This is a radical change in data gathering for health monitoring and assessment.

The preliminary results of PRIORI were recently published and have been reported upon by numerous media outlets. PRIORI has enormous potential and research continues. The next phase is to determine the sensitivity of the program and how early mood changes can be predicted.



For links to radio interviews and published stories on this project, visit prechterfund.org. Bookmark the site, follow us on Facebook and send it along to family and friends. Information changes lives!

A Special Thanks — and a Heads-Up for Those With an Eye for Style

Thanks to Suzen Kingston and the entire L.K.Bennett team in the Somerset Collection for their generous support of the Prechter Fund through two spectacular shopping events this past year.

Mark your calendars for the next event in their store on November 20th. Visit prechterfund.org for full details, and we'll see you at L.K.Bennett Somerset on November 20!



The Heinz C. Prechter
Bipolar Research Fund
at the University of Michigan
Depression Center

MISSION

To provide a repository of longitudinal clinical, genetic, and biological data to investigators worldwide for collaborative research on the causes, prevention, and treatment of bipolar disorder.

VISION

To personalize treatment of bipolar disorder and prevent recurrences to enable those with bipolar disorder to lead healthy and productive lives.

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