

# HOPE THROUGH RESEARCH

## WHAT CAUSES DEPRESSION?



**The HDRF Depression Task Force is Assembling a Picture of How Depression Develops in the Brain**

What causes clinical depression? You've probably heard it described as a "chemical imbalance" in the brain and something to do with a serotonin deficiency. This explanation is not inaccurate, but it is too simplistic.

As it turns out, the most important underlying cause of depression lies elsewhere. It involves our stress response; when our brain's fight or flight circuits get stuck in the "on" position for so long that it becomes toxic. Cells and circuits are thrown off balance, affecting sleep, memory, mood and behavior.

Our stress response involves hundreds

of important molecules and hormones that influence the brain and can change brain function. It's almost as if our stress response (our reaction to life events) can leave "scars" in the brain that are maladaptive and initiate the pathology of depression.

The Depression Task Force at HDRF is starting to discover a lot about these "scars" left by toxic stress in the brain, and also the genetic variations that make some of us more vulnerable to stress than others. This is leading to new ideas for treatment; we have one clinical trial underway right now and others in the pipeline.

No other team has been able to achieve the DTF's integrated approach. They are assembling a picture of how depression pathways can develop in the brain throughout our entire lives, from cradle to grave. That means they are embracing the full complexity of the brain from genes to molecules to cells and, ultimately, entire circuit networks.

Their leadership will influence the field for the next 50 years and beyond. Please read about their important discoveries in this newsletter.

# DEPRESSION TASK FORCE RESEARCH PROJECTS

## The Whole is Greater than the Sum of the Parts

The Depression Task Force's progress is the result of a unique collaboration. These HDRF scientists bring together a wide variety of research expertise and actively share unpublished data across multiple laboratories. While the progress outlined below is described separately for each scientist, in reality every member of the Task Force is involved directly in everyone else's endeavors. This remarkable effort has allowed us to study the neurobiology of depression from multiple perspectives. It also has provided the fortitude of community in the face of very intricate, precise and complex research.



### 1. A CLINICAL TRIAL FOR A POTENTIAL NEW CATEGORY OF MEDICATION IS UNDERWAY

**Dr. Jonathan Javitch**, a psychiatrist and biochemist at Columbia University, has identified a very specific pain receptor that malfunctions in patients with severe depression, which may blunt the ability to cope with the psychosocial stress of rejection in relationships (i.e. losing a job or promotion, ending a relationship). This has led to the trial of a compound that can fix the receptors through targeted action. The compound, known as tianeptine, represents a brand new category of antidepressant. Clinical trials began October 2020 at Columbia University and Mount Sinai Medical Center.



### 2. NEW GENES DISCOVERED THAT UNDERLIE TEMPERAMENT AND RESILIENCE TO STRESS

**Dr. Huda Akil**, a neurogeneticist at the University of Michigan, is concerned with how the temperament we are born with impacts our stress reactivity. Recently, she has discovered a critical new gene family that underlies differences in temperament, which in turn can make an individual exquisitely sensitive to stress, or resilient to stress. Her lab has discovered these emotionality genes in laboratory animals, and they are currently bridging these findings to humans.



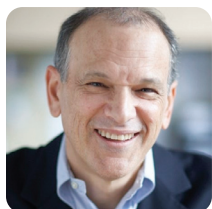
### 3. RESEARCH IN EUROPE SHOWS HOW STRESS IMPACTS CELLS IN THE FETAL BRAIN

**Dr. Elisabeth Binder**, a neurogeneticist and epigeneticist at Germany's renowned Max Planck Institute, is a leader in the genetic basis of depression, with a particular focus on the body's stress system. Her research shows that when prenatal brain cells are exposed to the stress hormone cortisol, many genes are altered that can increase the risk of depressive outcomes later in life. This process is strongly rooted in very small genetic variations, and our goal is match specific variations with specific effects on cell behavior. In the future, we want to be able to predict, by taking our genetic sequence at birth, whether we are at risk for developing major depression and apply the appropriate preventive measures based on that read-out.



### 4. IMPACT OF ADVERSE CHILDHOOD EXPERIENCE IS DIFFERENT IN MEN AND WOMEN

**Dr. Michael Meaney**, a neurogeneticist and epigeneticist at McGill University in Canada, shows how stressors in the environment contribute to depression by causing "epigenetic" changes—ones that turn genes on or off without altering the genes themselves. His work reveals how adversity early in life can permanently change the expression of key genes, and, as a result, increase the risk of developing depression in adulthood. Most recently, Meaney is studying how early life adversity affects men and women differently and creates different pathways of risk during a sensitive period of brain development. Understanding these mechanisms can help us develop precise early prevention strategies.



### 5. THE GENETIC BASIS OF RISK AND RESILIENCE THROUGHOUT LIFE

**Dr. Eric Nestler**, a molecular psychiatrist and neurobiologist at Mount Sinai, uses sophisticated mouse models of depression and post mortem brain tissue from depressed humans to map how stress produces lifelong chemical changes in key mood areas of the brain. Many of the changes are negative, causing hyper-reactivity to stress and risk for illness. Other changes, however, are positive and generate natural resilience to stress. This fascinates us, because we know that many cures and preventions for depression lie within our own bodies. They are just waiting to be discovered. Recently, this work has identified a potential new treatment to promote resilience which we will test in pilot clinical trials this year.



## 6. NEW FINDINGS MAY UNLOCK NEW TREATMENTS FOR DISORDERS LIKE PTSD THAT ARE ASSOCIATED WITH DISTRESSING MEMORIES

**Dr. René Hen**, a neuropharmacologist at Columbia University, is an expert in the hippocampus – a brain area that supports memory, mood and emotion. He has discovered specific nerve cells in the hippocampus that work carefully to code our experiences as good or bad, rewarding or fearful. In anxiety-related disorders like PTSD, memory coding goes awry, which can result in recurring distressing memories that come up completely out of context. Hen’s work points to ways we can diagnose broken memory circuits and intervene to treat them.



## 7. STUDIES IN PRE-FRONTAL BRAIN CIRCUITS SHOW NEW SUB-TYPES OF DEPRESSION AND DIFFERENCES IN MEN AND WOMEN

**Dr. Conor Liston**, a psychiatrist and neuroscientist at Weill Cornell Medicine, uses advanced neuroimaging techniques to study circuits in the pre-frontal cortex, a brain area that controls memory and regulates behavior. This part of the brain is heavily implicated in mood and anxiety disorders. His work in the past year shows that the pre-frontal cortex exerts its influence by maintaining a reserve of good memories that can be activated to elicit reward-seeking behavior. Liston has identified several circuit abnormalities that point to different subtypes of depression, which can now be used to target precision treatments to these subtypes. He has also identified distinct patterns of abnormal connectivity in men and women.



## 8. MAPPING BRAIN-WIDE CIRCUITS THAT UNDERLIE EMOTIONAL PROCESSING

**Dr. Kafui Dzirasa**, a neurobiologist and biomedical engineer at Duke University, is studying the role of entire brain circuits in mood and mood disorders. Dzirasa maps circuits by measuring brain waves – the electrical activity of cells and circuits. This approach allows us to see how different brain regions communicate and coordinate with one another to give rise to distinct emotional states such as motivation, anxiety, aggression, and the desire to engage socially with others. When the communication between brain regions is abnormal, this can foretell risk for depression. Dzirasa’s important discoveries point the way to a new class of precision diagnostics for depression based on large-scale measures of electricity in the brain.



## 9. REFINING KNOWLEDGE OF HUMAN NEURAL CIRCUITS IMPLICATED IN DEPRESSION

**Dr. Helen Mayberg**, a neurologist at Mount Sinai, is a pioneer in Deep Brain Stimulation (DBS) to treat severe, treatment resistant depression. In DBS, a pair of electrodes is implanted in a precise area of the brain and connected by wires to a pair of pulsing devices in the chest (akin to a cardiac pacemaker). The electrodes emit a kind of jamming signal to circuits in the brain known to be involved in depression, while leaving other circuits intact. Mayberg’s groundbreaking work allows the Depression Task Force to better understand how all of the circuits of the brain connect and interact. As more clear and precise circuit knowledge emerges from the group, Mayberg is in turn able to refine the areas she targets with DBS treatment.

### SUPPORT HDRF

100% of all donations go directly to research into the origins, diagnosis, treatment and prevention of depression and its related mood disorders including: post-partum depression, post-traumatic stress disorder, anxiety disorders, and suicide.

HDRF is a non profit 501(c)(3) public charitable organization.  
All donations are tax-deductible to the fullest extent of the law.

Visit us at [hopefordepression.org](http://hopefordepression.org)

# OVER 1,000 PARTICIPANTS JOINED IN THE 2021 WINTER VIRTUAL RACE OF HOPE!



**Co-Grand Marshals Scott Snyder and Audrey Gruss**

More than 1,000 men, women and children nationwide raised over \$365,000 for the **Virtual Race of Hope Palm Beach/Winter 2021**.

Although we could not gather in a common location, we marked the official Race day with a LIVE video broadcast from Palm Beach on Saturday, February 27.

HDRF Founder **Audrey Gruss** and Advisory Board member **Scott Snyder**, both Grand Marshals, hosted the live broadcast. They greeted participants who were watching the program on their

phones before starting out on their races all over the country.

Many racers raised funds from their friends and family. Top fundraising team, **Tigers for Hope** from New York, raised over \$5,000. Top fundraising individual, **McKinley Frantz** from Connecticut, raised over \$2,000.

Thank you again to our wonderful Palm Beach Committee Members and Corporate Sponsors for making this virtual event JUST as successful as our regular Palm Beach Race.



**Longtime corporate sponsors James R. Borynack and Adolfo Zaralegui of Findlay Galleries**



**Music legend Gloria Estefan made a special appearance**



**Runners from across the country posted photos on our Race page**



**Peggy Schnack of Concord, NH**

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