intersections

Brain Research Foundation

2018-2019 Impact Report

impact

Brain Research Foundation funds research that impacts our understanding of all diseases and disorders of the brain.

ALS (LOU GEHRIG'S DISEASE)

AGE-RELATED MACULAR DEGENERATION (AMD)

AGGRESSIVE DISORDER

ALCOHOLISM

ALZHEIMER'S DISEASE

ANOREXIA NERVOSA

ANXIETY DISORDERS

APHASIA

ARTERIOVENOUS MALFORMATION

ASPERGER SYNDROME

ATTENTION DEFICIT DISORDER

AUTISM SPECTRUM DISORDER

BATTEN DISEASE

BELL'S PALSY

BIPOLAR DISORDER

BLINDNESS

BRAIN ANEURYSM

BRAIN CANCER

BRAIN DEVELOPMENT

BRAIN TUMORS

BULIMIA

CEREBRAL PALSY

CHARCOT-MARIE-TOOTH DISEASE

CONCUSSION

CONDUCT DISORDER

CREUTZFELDT-JAKOB DISEASE

DANDY-WALKER SYNDROME

DEMENTIA

DEPRESSION

DEVELOPMENTAL DISORDERS

DOWN SYNDROME

DYSTONIA

EATING DISORDERS

ENCEPHALOPATHY

EPILEPSY

ESSENTIAL TREMOR

FATAL FAMILIAL INSOMNIA

FRAGILE X SYNDROME

FRONTOTEMPORAL LOBAR DEGENERATION

GUILLAIN-BARRÉ SYNDROME

HEMIFACIAL SPASM

HUNTINGTON'S DISEASE

LEARNING DISABILITY

LEWY BODY DEMENTIA

LOCKED-IN SYNDROME

MANIC-DEPRESSIVE ILLNESS

MENINGITIS

MENTAL RETARDATION

MIGRAINE HEADACHES

MOTOR NEURON DISEASE

MULTIPLE SCLEROSIS

MUSCULAR DYSTROPHY

MYASTHENIA GRAVIS

NARCOLEPSY

NICOTINE ADDICTION

NEUROPATHY

OBSESSIVE-COMPULSIVE DISORDER

OPIOID ADDICTION AND DEPENDENCY

PANIC DISORDER

PARKINSON'S DISEASE

PICK'S DISEASE

POST TRAUMATIC STRESS DISORDER (PTSD)

PRION DISEASE

RESTLESS LEGS SYNDROME

RETT SYNDROME

SCHIZOPHRENIA

SLEEP APNEA

SPINAL CORD INJURY

SPINAL MUSCULAR ATROPHY

STROKE

SUBSTANCE ABUSE DISORDERS

TAY-SACHS DISEASE

TOURETTE SYNDROME

TRANSIENT ISCHEMIC ATTACK

TRAUMATIC BRAIN INJURY (TBI)

TRIGEMINAL NEURALGIA

TUBEROUS SCLEROSIS

WILLIAMS SYNDROME

intersections

- unexpected connections yield new discoveries
- bold researchers pivot in new directions
- new tools open old mysteries

Breakthroughs in science don't all come from a single, predictable path. Sometimes researchers start with one idea but are led in a different direction by their results or the results of other scientists. Or a new tool enables scientists to approach an old question in an innovative way.

Brain Research Foundation understands that advances in science often happen where ideas, tools, and different scientists' work intersect. That's why for more than 65 years the Foundation has focused on funding visionary scientists who see opportunities in forging new paths.

BRF grants are often the bridge these ground-breaking scientists need to get a new idea off the ground, to build new tools, or to generate the data necessary to secure more funding. By supporting ground-breaking work BRF helps set the trajectory of brain research and builds momentum towards discoveries that will yield major advances in neuroscience.

contents

Dear Friends,

After more than six decades of supporting neuroscience, Brain Research Foundation (BRF) and its mission continue to adapt and grow to fund the most impactful research within the ever-advancing fields of science. When the Foundation began in 1953, we were supporting "brain research," but since then our areas of funding have expanded, evolved and intersected.

Both BRF and the study of the nervous system grew in the second half of the twentieth century and into the twenty-first century. The scope of neuroscience has broadened, and research has intensified, primarily because of the advancements in scientific techniques such as molecular biology, genetics and brain imaging. Because neuroscience is such a rapidly progressing field, today it encompasses a wide variety of branches, including **behavioral neuroscience, molecular neuroscience, neuroanatomy, neurophysiology, neurobiology, neurochemistry, neuropharmacology, neuropathology, psychiatry, neurology, neurosurgery, neuroimaging, clinical psychology, and others**.

BRF has funded research in all these areas to impact scientific discovery. It is this array of research that is leading to important information on how the human brain functions and how the nervous system develops and matures through life. As we come to understand how the nervous system works, we begin to repair it.

The Foundation has always provided unwavering support for new directions in research. Our contributions to scientists through our successful grant programs–Fay/Frank Seed Grants and Scientific Innovations Award–have generated findings that impact the work of our grantees and enable them to leverage those findings into other studies. The list of our latest recipients illustrates the wide variety of science that we fund to enhance the quality and amount of information about the nervous system, creating the necessary knowledge from which scientists can continue to build.

We support pioneering research setting the trajectory for discoveries and eventual cures.

In this report, we examine how funding the pilot stage of an innovative scientific idea can have enormous rewards. Although we only share with you four scientists' stories, we are intensely proud of all our investments and will continue to fund top-quality science that will produce tangible results in the years to come.

Working alongside Peter Pond, Chairman of the Board of Trustees has been a privilege, and I join him in thanking the entire Board, the Young Leadership Board, Scientific Review Committee and friends and donors for their dedication to our mission.

Neuroscience holds great promise for understanding devastating illnesses like Alzheimer's disease, epilepsy, stroke, schizophrenia, multiple sclerosis and many more. Together we will continue to fund the future of neuroscience and set the trajectory for new treatments and eventual cures.

Sincerely,

Terre A. Constantine, Ph.D.
Executive Director and CEO

Every two years we publish an annual report, but this year we've decided call it an "Impact Report" instead. We believe this new title is far more fitting for our organization and the extraordinary neuroscience research it funds.

One of the reasons that the research we fund is so impactful is our unique approach of not limiting ourselves to one disease or condition. While we list many of these diseases and conditions on the inside of the front cover, it is just as important that we fund studies that try to determine how we learn, what creates memories, how the gut affects brain health and especially what happens to the brain as we age.

None of this would be possible without our friends and donors. I am sincerely grateful for your support. Additionally, I would like to thank the following groups and individuals for their on-going commitment to BRF:

- The Board of Trustees, who continue to tell the story and the mission of BRF to their friends, family and colleagues to broaden our reach and the scope of our support.
- The Young Leadership Board, who in four short years took their annual event from raising $40,000 to raising over $90,000. The Board of Trustees is so grateful for your energy and enthusiasm and for plotting a trajectory for the next generation of philanthropists through fundraising and awareness.
- The Scientific Review Committee, who annually review over 200 Letters of Intent, narrowing it down to about 40-50 applications and then recommending the best research projects to fund in the country. It's a daunting task but incredibly important and we are grateful for your guidance and expertise.
- The BRF office of Dr. Terre A. Constantine, Executive Director and CEO and Sandra Jaggi, Director of Philanthropy for running such a tight ship. This is crucial to our ability to ensure that every dollar raised goes directly to research and educational programs, while also ensuring that for the past two years we've received a 4-star designation in Charity Navigator. Thank you for staying focused on how best to preserve the legacy of the BRF while looking forward to growing into the future.

In the pages that follow you will learn more specifics about our high-impact research including a special opioid relapse reduction initiative that was generously funded by Blue Cross Blue Shield Association and generated some very important results. You will also hear from a Young Leadership Board member about why he joined the board. I hope that you find this report interesting and our research impactful. Thank you for your support.

Yours Sincerely,

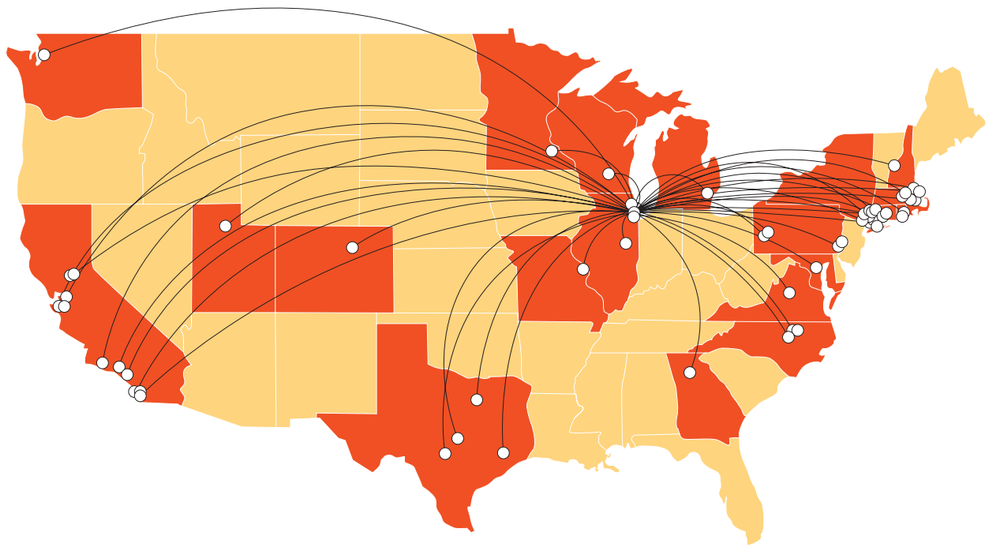
Peter Pond
Chairman, Board of Trustees

a transformational catalyst

The majority of BRF's donors are individuals who share the Foundation's passion for advancing brain research. 100% of every dollar donated goes towards funding research and educational programs because BRF's small staff and lean operational costs are supported by investment income. This allows donations to go further and enables the innovative scientists it funds to do more.

To date, BRF has provided more than $46 million in grants with a focus on funding inventive scientists trying to get unique ideas off the ground. Every one of those grant dollars leads to about $22 in additional funding for the investigator bringing these cutting-edge labs many steps closer to a breakthrough.

By making the most of each donation and funding projects most likely to have a transformative impact, BRF is truly a catalyst for new discoveries in brain science.



BRF has funded visionary scientists working across the United States. By supporting pioneering research, the Foundation is setting the trajectory for discoveries and eventual cures.

the trajectory of discovery

Sometimes the hardest part of science is just getting started. For investigators starting a lab or trying to shift to a new line of investigation it can be hard to get the necessary startup funds. Many traditional funders like the National Institutes of Health focus on funding established labs and lines of inquiry that have already led to discoveries. But that can impede innovation. It may prevent talented young researchers with fresh ideas from getting a good start and it can steer experienced researchers away from taking a bold new path.

That's why BRF focuses on providing researchers start-up funds for new investigations. This enables experienced researchers to pivot in a new direction and younger scientists to generate the data required to receive additional funding that will propel their ideas further.

Beyond expanding the research of principal investigators, BRF grants also help launch the careers of graduate students and post-doctoral fellows in our grantees' laboratories. Often, it's these young scientists who are ready to take on the challenge of learning a new technique or taking on an ambitious project. As they gain experience they help their principal investigators answer essential questions about neuroscience and build new tools. Along the way, these young researchers are gaining the momentum necessary to get their own careers off the ground and start their own laboratories at other institutions, expanding the influence of BRF grants and growing the field.

BRF's start-up focused funding strategy not only enables todays' breakthroughs, but also lays the foundation for the discoveries of the future by kickstarting the careers of ambitious new generation of investigators unafraid to try new things and answer big questions.

BRF recognizes that discoveries at the intersections of several fields often have the greatest potential to lead to fundamental insights about the brain.

intersections= opportunities

While many organizations focus on researchers studying a specific disease, BRF recognizes that breakthroughs often come from unexpected places. That's why the Foundation doesn't just focus on one disease, but instead funds the most visionary scientists working on potentially transformative projects in neuroscience.

In fact, the work of the BRF grantees we highlight in this report occurs at unexpected intersections:

- Genetics and Neurodevelopment
- Microbiome and Autism Spectrum Disorders
- Neurodegenerative Disease and Addiction

That's no accident. BRF recognizes that discoveries at intersections often have the greatest potential to lead to fundamental insights about the brain–the kind of insights that will help individuals with many different disorders that affect the brain. This is especially true with the emergence of new disciplines like genomics, proteomics, microbiomics, metabolomics, and transcriptomics. These new approaches enable scientists to systematically study the brain without preconceived notions about what the outcomes might be.

Recognizing the tremendous opportunities at intersections between fields, BRF doesn't shy away from researchers taking unconventional paths. Whether it's changing paths to study a new disease or to try a new tool, BRF recognizes the importance of researchers willing to be bold and try a new direction.

In this report, BRF highlights brilliant grantees and a passionate donor who recognize the importance of looking for answers that transcend a single brain disease.

the path to progress

BRF Fay/Frank Seed Grants provide early career scientists the support they need to begin to test their ideas and solidify their academic careers. Seed Grants provide $80,000 over two years and enable young investigators to generate the preliminary data they need to compete for larger grants from traditional funding sources such as the National Institutes of Health.

The BRF Scientific Innovations Awards are designed to support established basic or clinical neuroscience researchers taking a chance on an innovative project that could yield big gains. The awards provide $150,000 over two years to support projects that may be viewed as too speculative by some traditional funders but have a high potential to yield important insights in a short period of time.

The path to being awarded a BRF grant starts with a nomination from the investigator's university. Nominees for BRF grants represent the brightest talent at universities around the country. These talented nominees describe why they think their project could help lead to new insights on neuroscience or diseases affecting the brain.

The BRF's Scientific Review Committee (SRC), which is made up of leading neuroscientists with diverse backgrounds, review these proposals. Then they select those scientists and projects with the greatest potential. The SRC not only looks for projects that could lead to immediate breakthroughs in neuroscience, but projects that could yield collateral benefits for many years to come by producing new research tools or launching the careers of promising young scientists.

So far, this venture capital-like approach has had tremendous success advancing neuroscience and in helping improve care for patients with brain disease. Projects BRF has funded have led to improved neural prosthetics for paralyzed patients, the development of a blood flow sensor for the brain to help detect stroke or other brain injuries, a new presurgical approach for epilepsy patients, and a strategy using immune cells to target brain tumors.

2018 FAY/FRANK SEED GRANT RECIPIENTS

ANDRE BERNDT, PH.D.

University of Washington

Monitoring Communication in Neuronal Networks in Real Time and at Single Cell Resolution

APPLICATIONS: DRAVET SYNDROME, AUTISM, EPILEPSY

DENISE CAI, PH.D.

Icahn School of Medicine at Mount Sinai

Investigating the Role of Negative Valence in the Temporal Dynamics of Memory-Linking

APPLICATIONS: ANXIETY, MEMORY, PTSD

WEIZHE HONG, PH.D.

The Regents of the University of California, Los Angeles

Dissecting the Organization and Function of Social Behavioral Circuits in the Amygdala

APPLICATIONS: SOCIAL BEHAVIOR, AUTISM SPECTRUM DISORDERS, DEPRESSION, MENTAL ILLNESS

The Dodge H. Teague, Jr. Seed Grant

TAKASHI KITAMURA, PH.D.

University of Texas Southwestern Medical Center

Neural Circuit Mechanisms of Behavior-Dependent Representation for Space and Time

APPLICATIONS: LEARNING AND MEMORY, OPTOGENETICS, HIPPOCAMPUS

SHENG-HAN KUO, M.D.

Columbia University

Aberrant Synaptic Organization in Tremor Disorders

APPLICATIONS: TREMOR, CEREBELLUM, SYNAPSES

JENNIFER PHILIPS-CREMINS, PH.D.

University of Pennsylvania

Elucidating the Role for 3D Genome Topology Disruption in Trinucleotide Repeat Expansion Disorders

APPLICATIONS: EPIGENETICS, CHROMATIN, FRAGILE X SYNDROME

Women's Council Seed Grant

DAVID SCHOPPIK, PH.D.

New York School of Medicine

A Novel Whole-brain Method for In Vivo Imaging of Progressive Neurodegeneration

APPLICATIONS: NEURODEGENERATION, PROGRESSIVE SUPRANUCLEAR PALSY

2019 FAY/FRANK SEED GRANT RECIPIENTS

ROBERT A. HILL, PH.D.

Dartmouth College

Mechanisms of myelin degeneration and clearance in the live brain

APPLICATIONS: MYELIN, NEURODEGENERATION, MULTIPLE SCLEROSIS, STROKE

Carl & Marilynn Thoma Foundation Seed Grant

LINDSEY MACPHERSON, PH.D.

University of Texas at San Antonio

Visualizing chemosensory connectivity: getting a "GRASP" on taste synapses in the tongue and gut

APPLICATIONS: TASTE, GUT-BRAIN COMMUNICATION

KAI MILLER, M.D., PH.D.

Mayo Clinic

An implanted brain-computer interface for ALS patients

APPLICATIONS: AMYOTROPHIC LATERAL SCLEROSIS (ALS), BRAIN-COMPUTER INTERFACE

TIFFANY SCHMIDT, PH.D.

Northwestern University

A modular system for temporal and cell-type specific manipulation of neural circuits

APPLICATIONS: VISION, LIGHT, RETINA, BEHAVIOR

Women's Council Seed Grant

IKUKO SMITH, PH.D.

University of California, Santa Barbara

Active dendritic processing of sensory inputs in vivo

APPLICATIONS: AUTISM, SENSORY PERCEPTION

KATHLEEN SMITH, PH.D.

University of Colorado, Denver

Excitatory and inhibitory synapse communication in synaptic plasticity

APPLICATIONS: AUTISM, SCHIZOPHRENIA, EPILEPSY

MEGAN WILLIAMS, PH.D.

University of Utah

A new class of autism-associated GABA neurons in memory precision

APPLICATIONS: LEARNING AND MEMORY, AUTISM, MENTAL ILLNESS, EPILEPSY

Yound Leadership Board Seed Grant

ERIC YTTRI, PH.D.

Carnegie Mellon University

Revealing how value is translated into action with simultaneous single neuron and multi-area resolution

APPLICATIONS: OBSESSIVE COMPULSIVE DISORDER, PREFRONTAL CORTEX, LEARNING

2018 SCIENTIFIC INNOVATIONS AWARD RECIPIENTS

RYOHEI YASUDA, PH.D.

Max Planck Florida Institute for Neuroscience

Imaging dynamics of endogenous protein interactions in single dendritic spines

APPLICATIONS: MENTAL ILLNESS, LEARNING, MEMORY

XINYU ZHAO, PH.D.

University of Wisconsin, Madison

Interrogating Experience-Induced Gene Regulatory Network Dynamics in Interneurons

APPLICATIONS: AUTISM, BIPOLAR DISORDERS, SCHIZOPHRENIA

2019 SCIENTIFIC INNOVATIONS AWARD RECIPIENTS

VIKAAS S. SOHAL, PH.D.

University of California, San Francisco

Do dopamine signals promote flexible behavior by recruiting synchronized brain rhythms?

APPLICATIONS: LEARNING, SCHIZOPHRENIA

MICHAEL E. TALKOWSKI, PH.D.

Harvard Medical School

Does the three-dimensional organization of the genome hold new insights into neurodevelopmental disorders?

APPLICATIONS: PSYCHIATRIC DISORDERS, NEURODEVELOPMENTAL DISORDERS, CRISPR

BRF/BCBSA OPIOID INITIATIVE RESEARCH AWARDS

AMANDA L. PERSONS, PH.D.

Rush University Medical Center in Chicago

Discovering alternate targets in the brain that may help reduce opioid craving during recovery

BARBARA WASZCZAK, PH.D.

Northeastern University

Testing whether nasal delivery of the DNA that encodes GDNF reduces relapse-like behavior in rats administered opioids

BRF's opioid initiative leverages research intersections to tackle a crisis

$78.5 billion/year is the total economic burden of prescription opioid misuse in the US, including the costs of healthcare, lost productivity, addiction treatment, and criminal justice involvement.

up to **90%** of opioid users who seek treatment experience relapse

Every day, **130 people** die from opioid-overdoses in the United States

Nationally, **2.1 million people** currently have an opioid use disorder

It's estimated that **80%** of people who use heroin first misused prescription opioids

The midwest region saw a **70% increase** in opioid overdoses from July 2016 through September 2017

The ongoing opioid epidemic is one of the most devastating public health crises the United States has ever faced. It's estimated that more than 130 people die from opioid-overdoses each day in the US, and 2.1 million people currently have an opioid use disorder[1]

To help combat the crisis, BRF formed the Opioid Advisory Committee (OAC) in 2017 made up of leading scientific experts on opioid dependency and addiction. **The committee recommended that BRF focus on funding research aimed at reducing relapse.** Nearly a staggering 90% of those who seek treatment for opioid use disorders experience a relapse, and there is an urgent need to develop new relapse prevention therapeutics.

"BRF's OAC has shined a light on the possibility that an opportunity may exist today that will help people on the path to recovery from opioid addiction from sliding back into the grasp of chemical addiction," said Dr. Terre A. Constantine, Executive Director and CEO of BRF. "The scope of this crisis is such that even a modest, positive effect on relapse would be of monumental benefit."

With generous funding from the Blue Cross Blue Shield Association, BRF awarded two opioid initiative grants in 2018 to two researchers who are working to develop and repurpose drugs that could prevent the opioid cravings that lead to relapse. Like many of the scientists BRF funds, these scientists are also looking for insights at the intersection of research on different brain diseases to accelerate progress.

Their work is essential to bringing an end to the opioid crisis and relief to those in recovery, their loved ones, and their communities.

Members of Brain Research Foundation's OAC were chosen for their experience and expertise in the area of opioid addiction.

The OAC identified the focus on reducing relapse and reviewed and recommended the proposed projects to receive funding.

Saira A. Jan, M.S., Pharm D.
Director of Pharmacy Strategy and Clinical Integration
Horizon Blue Cross Blue Shield of New Jersey
Clinical Professor, Rutgers State University of New Jersey

Jack Bergman, Ph.D.
McLean Hospital/Harvard Medical School
Associate Professor of Psychobiology in the Department of Psychiatry

Terre A. Constantine, Ph.D.
Executive Director and Chief Executive Officer
Brain Research Foundation

Jonathan L. Katz, Ph.D.
Senior Investigator
Chief, Psychobiology Section (Ret.)
National Institute on Drug Abuse

Frank Vocci, Ph.D.
President
Friends Research Institute, Inc.

[1]US Department of Health and Human Services. About the Opioid Epidemic. https://www hhs.gov/opioids/about-the-epidemic/index.html.

a new path to beat addiction

Addiction causes biochemical and structural changes in the brain. By funding research that reveals those changes and finds ways to reverse them, BRF hopes to help stem the ongoing epidemic and provide relief for the individuals and families affected by it.

For patients recovering from opioid use disorder there are three drugs currently available for treatment: methadone, buprenorphine, and naltrexone. All three of these drugs attach to opioid receptors in the brain preventing heroin or prescription opioid drugs from binding and helping to reduce craving in patients. But given the ongoing opioid crisis and the high rate of relapse there is an urgent need for more options.

"Treatment is not one size fits all–what may work for one patient may not work for another," said Amanda L. Persons, Ph.D., Associate Professor and Director of the Facility for Rodent Models of Human Brain Disease in the Center for Compulsive Behavior and Addiction at Rush University Medical Center in Chicago. Dr. Persons is one of two recipients of opioid research grants from BRF in 2018.

Dr. Persons and her collaborator, Dr. Celeste Napier, are looking for alternate targets in the brain that may help reduce opioid craving during recovery. The team's previous work studying relapse to methamphetamine use in rats led them in a promising direction. They discovered that targeting a serotonin receptor called 5-HT2CR using the antidepressant mirtazapine reduces relapse-like behavior in rats trained to self-administer methamphetamine.

"It's kind of like the 5-HT2CR receptor is always turned on [in these animals] and mirtazapine is able to shut it off," she explained. The finding was particularly exciting because mirtazapine has already been shown to be safe, well-tolerated, and effective for depression treatment in humans.

"Repurposing an existing drug shaves a lot of time off the process of getting medications into the clinic to test them in humans," Dr. Persons explained.

To begin to test whether mirtazapine might also help prevent relapse in opioid use disorder, Dr. Persons and her team tested using mirtazapine in rodents conditioned to associate a specific environment with morphine. They found that rodents treated with mirtazapine were less likely to spend time in the environment where they received morphine–the rats were spending less time seeking the drug. Such environmental cues have been shown to trigger drug craving and relapse in humans as well.

Dr. Persons' findings are particularly exciting because the drug she is investigating to treat opioid relapse is already approved for use in humans.

"Relapse to drug taking is not so much about the drug itself anymore," Persons explained. Instead, it is often about the associations a person has developed between the feeling they got taking a drug and the places, people, and paraphernalia they associate with it. "Maybe through cognitive behavioral therapy and pharmacological therapy, we can temper down those cravings and make them manageable for people," she said.

The grant from BRF allowed Persons and her team to take the next step by testing whether mirtazapine can reduce relapse-like behavior in rats trained to self-administer heroin, a gold-standard model for addiction research. They are also documenting the changes that occur in the 5-HT2CR receptors in response to heroin use, relapse, and mirtazapine treatment.

Dr. Persons plans to publish her results soon. She hopes that her work will not only lead to more treatment options, but also help destigmatize relapse–a goal BRF shares. Relapse is common in many other chronic conditions as well, Dr. Persons explained, but patients who experience a relapse to substance abuse often face judgement.

"Addiction is a brain disease," Dr. Persons said. "It causes biochemical and structural changes in the brain."

By identifying and helping to fund research that reveals those changes and finds ways to reverse them, BRF hopes to help stem the ongoing epidemic and provide relief for the individuals and families affected by it.

Funding for this research was generously provided by BCBSA

the intersection of Parkinson's disease and addiction

Dr. Waszczak's work is a powerful example of why BRF's non-specific disease approach is so effective. Often breakthroughs come from unexpected places.

A detour in Parkinson's disease research led Barbara Waszczak, Ph.D., professor in the Department of Pharmaceutical Sciences at Northeastern University in Boston, in an unexpected direction–opioid abuse relapse research.

Dr. Waszczak had been studying glial cell-derived neurotrophic factor (GDNF) as a potential treatment for Parkinson's disease for about a decade. Parkinson's disease kills brain cells that produce the neurotransmitter dopamine, which is released during pleasurable activities. Though it is normal for dopamine-producing brain cells to die off across the course of the human lifespan, the process is accelerated in Parkinson's disease. Evidence shows that GDNF increases the survival, size, and dopamine-production of these cells.

"If GDNF could stop whatever is killing these neurons, you could arrest disease progression and maybe even promote some recovery of the cells that haven't yet died," she said. "It could stop the disease in its tracks."

The challenge has been finding a way to get GDNF into the brain. Some other research labs have injected GDNF directly into the brain, but clinical trials of that approach failed to show a benefit. "It wasn't clear whether they were succeeding in getting GDNF into the brain appropriately," Dr. Waszczak explained. But she and her colleagues had an alternate delivery method.

"Our unique approach was to use intranasal delivery of GDNF," she said. "It doesn't require a surgical procedure. It relies upon the fact that things can travel from the nose into the brain by getting through small

spaces between olfactory neurons that enter the nasal cavity and project into the brain."

Her team published studies in the early 2000s showing that intranasal delivery of GDNF in rats with a Parkinson-like condition protected the dopamine-producing cells. Dr. Waszczak later refined her GDNF delivery approach by partnering with company called Copernicus that makes nanoparticles of the DNA that encodes GDNF.

"We thought a better approach might be to use intranasal delivery to get the gene into the brain so that it could produce levels of GDNF that might be neuroprotective for a longer period of time than a single intranasal dose of the protein," Dr. Waszczak said. They even showed this new delivery method helped rats with a Parkinson-like disorder. But she struggled to find funders to support her work on GDNF as a treatment because of the earlier failed clinical trials.

It seemed like an insurmountable roadblock. But then she discovered evidence that GDNF might be useful for treating a range of other brain diseases, including addiction. Dr. Waszczak was awarded a 2018 Opioid Initiative grant from BRF to test whether nasal delivery of the DNA that encodes GDNF reduces relapse-like behavior in rodents administered opioids. Her work is almost complete, and the data so far suggest it works.

She's begun applying for grants to conduct the studies necessary to confirm her findings in rodents, which would pave the way to test this therapy in people with opioid addiction. She is also collaborating with another scientist to test a theory about why it works: "Overuse has caused the dopamine-producing neurons to become deficient," she proposed. "That's why people who've been using drugs for a while can't stop taking them. They need to take them in order to feel any kind of positive rewarding feelings. If GDNF could restore the dopamine levels in the brains of these people, they might stop craving and be able to recover."

Dr. Waszczak's project is almost complete and the data indicate that her innovative hypothesis may lead to a novel treatment for addiction.

Dr. Waszczak's work is a powerful example of why BRF's approach is so effective. Often breakthroughs come from unexpected places, in this case at the intersection of Parkinson's disease research and addiction research.

"Without the BRF grant I would not have pursued this," she said. "It would've been something I considered outside my domain. The BRF grant gave me the confidence that this was a good idea and the momentum to take it forward and to try a new area of science."

Funding for this research was generously provided by BCBSA

answers at the gut microbiome-brain interface

Learning more about how microbes and neurons communicate with one another may reveal new molecular targets for developing better treatments for neurological diseases.

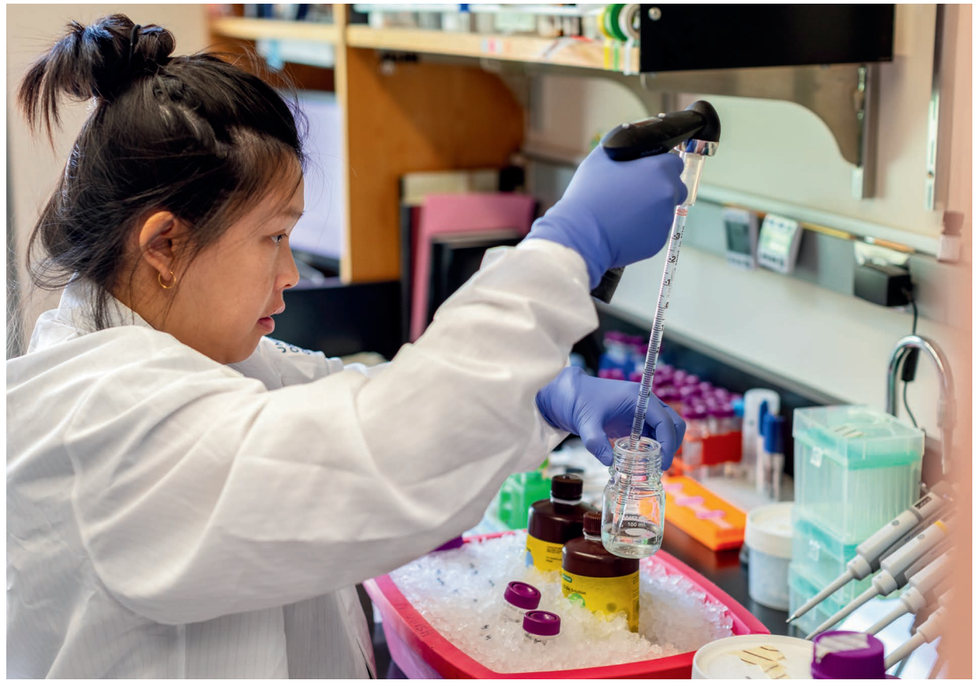
The brain has long been viewed as the body's control center because it integrates information from each body system and directs the appropriate responses. Emerging evidence suggests that the trillions of bacteria living in the human gut may strongly influence brain activity and that these interactions play a pivotal role in brain health and disease.

"Microbes have the remarkable capacity to modulate brain activity and behavior, which suggests that elucidating the interactions between microbes and the nervous system will provide new insights into brain development and function, and potentially uncover strategies for treating complex nervous system disorders," said Elaine Hsiao, Ph.D., assistant professor at the University of California-Los Angeles Departments of Integrative Biology & Physiology and Microbiology, Immunology & Molecular Genetics.

Dr. Hsiao was awarded a BRF Fay/Frank Seed Grant that will enable her team to begin to systematically test how various gut microbes communicate with specific types of brain cells called neurons.

"We are trying to decode how different types of gut microbes signal to neurons and the different types of messages that are being relayed to the brain to influence behavior," she explained.

The grant will also help the team build the tools necessary for such an ambitious investigation. This includes creating a system that enables them to record electrical signals from living brain cells in animals whose guts have been infused with different bacteria or molecules produced by gut bacteria. They've also established an imaging method to watch brain cells firing in real-time using fluorescent light.



Dr. Hsiao's findings have already led to her participation in a larger project with funding in excess of $5.5 million.

"We hope that learning more about how microbes and neurons communicate with one another will reveal new molecular targets for developing better treatments for neurological diseases," she said.

Dr. Hsiao's interest in the intersection between the gut microbiome and the brain was piqued by her graduate studies on the interaction between the immune system and the nervous system in autism spectrum disorders. That led her to appreciate how vital the microbiome is to normal immune function, metabolism, gut health, and nervous system function.

"I've always been intrigued by connections between the brain and the body, especially since so many neurological diseases include symptoms outside of the brain," Dr. Hsiao said. For example, inflammatory bowel disorder is highly co-occurring with Parkinson's disease, and often precedes its diagnosis by decades, leading researchers to study whether intestinal disturbances can contribute to its development.

Research in Dr. Hsiao's lab now spans the fields of neuroscience, immunology, and the emerging field of gut microbiota research. She and her team use a wide range of techniques including brain imaging and genetic sequencing in their investigations.

"I love multidisciplinary research because it merges the very different perspectives, approaches and cultures of different disciplines," she explained. "I think this is important for studying nature, which has no separate fields or boundaries."

Like many of the researchers BRF elects to fund, Dr. Hsiao's work has the potential to transform our understanding of the brain and nervous system, which may have implications for many brain diseases. She and her team have already published studies exploring the role of the microbiome in autism spectrum disorders, seizures, psychiatric conditions, movement disorders, addiction, and brain development.

"At the root of all of our studies are really fundamental questions about how different systems, like the microbiome, immune system and nervous system, interact with each other," Dr. Hsiao said. "We hope that the principles that emerge from these basic questions will apply to brain and body interactions across a wide range of neurological disorders."

the intersection of form and function

Disruptions in DNA's 3D-structure linked to neurodevelopmental brain disorders.

A series of cases in which children with developmental brain disorders had no apparent changes in their genes led Harvard University's Michael Talkowski, Ph.D. and his team in a new direction. They discovered that the children had changes in the 3-dimensional structure of their DNA that altered gene activity without changing the gene's themselves.

"It led us to think that perhaps this happens more widely and pervasively throughout the genome," said Dr. Talkowski, associate professor of neurology, Psychiatry and Pathology at Harvard University and member of Harvard's Center for Human Genetic research. Dr. Talkowski and his team were awarded a 2019 BRF Scientific Innovations Award grant to help them begin to determine how often such structural changes in DNA contribute to neurodevelopmental disorders.

For more than a decade, Talkowski and his colleagues have documented the ways that changes in genes can contribute to diseases like autism spectrum disorders. Over time, they've come to appreciate that the way DNA is folded up within the nucleus of cells is more than just a convenient storage method–it's a way to control which genes are expressed. So, as they continue to hunt for disease-linked genes they are also working to understand how the 3D structure of folded DNA may also contribute to brain disease.

BRF's grant has been a catalyst for Dr. Talkowski's team to take the research that they were doing in an entirely new direction.

"It's the next frontier," he said. He explained that genes make up just 2% of the human genome so understanding what the other 98% does is essential.

The BRF grant will enable a Ph.D. student in Dr. Talkowski's lab to undertake an ambitious project. She will systematically use state-of-the-art CRISPR-Cas9 technology to make cuts in noncoding DNA that change the 3D structure of the DNA and then use RNA sequencing to document how each change alters gene expression in brain cells grown in the laboratory from human stem cells. "This grant has been a catalyst for us to take the research that we were doing in an entirely new direction," he said.

"We're going to delve into the biology of the genome by using CRISPR-Cas9 to break the genome apart," Dr. Talkowski explained. "The study will be the first to directly model structural rearrangements of the genome in human brain tissue to determine whether disrupting noncoding segments of DNA responsible for proper 3D folding can be as damaging as direct gene mutations."

So far, the team's preliminary data suggest that such structural changes in DNA may cause neurodevelopmental disorders by altering the activity of important genes. This may eventually help scientists identify risk factors that may contribute to such harmful changes in early development and possibly find ways to prevent them.

The team's preliminary data suggest that structural changes in DNA may cause neurodevelopmental disorders by altering the activity of important genes.

The research is a great example of how BRF's funding strategy may lead to major changes in the direction of brain research. Dr. Talkowski's non-disease specific approach to understanding genome biology is likely to yield discoveries that will aid patients with many different psychiatric and neurodevelopmental disorders.

"Being agnostic to hypotheses that define what should happen, and just asking the question of what does happen, that's been beneficial," Dr. Talkowski said.

finding comfort in the search for cures

More than 1 in 6 individuals worldwide has a disorder that affects the brain,[1] which means that many families have a loved one who is impacted. Ben Usem's family is one of them.

Ben's mother was diagnosed with a benign meningioma brain tumor during a routine eye screening when he was just 12 years old. She successfully underwent surgery to remove the tumor. But she later developed an essential tremor, which led to an diagnosis of Parkinson's disease that was unrelated to her tumor or tremor. Around the same time, his father experienced a stroke. It was scary time for the family. But thanks to excellent care, both of Ben's parents continue to thrive, working fulltime.

"They're both living fulfilling, great lives," Ben said. His family's experiences motivated him to join the BRF's Young Leadership Board (YLB) while studying accounting and risk management as an undergraduate at the University of Wisconsin-Madison. The YLB was launched in 2017 to give 22- to 40-year-olds a way to engage with the organization and its mission.

"I wanted a way to get involved while not being a scientist and not having a lot of money yet to give to the cause," he said. That commitment to wanting to advance brain research motivated by having a loved one affected by brain disease is shared by many of BRF's donors and volunteers. Ben believes that BRF's disease-agnostic approach creates an opportunity for people with a wide range of experiences to unite in working toward a common goal and increases the likelihood that BRF's funding and support will yield breakthroughs in care.

"The fact that BRF doesn't focus on just one disease and encourages collaboration and funding for everyone allows for more cross-disciplinary discussion," he said. "This will result in more discovery."

Participating in the YLB has allowed Ben to help other people his age who may not be directly affected learn more about brain diseases through events like the annual *Let's Put Our Heads Together* fundraiser. The board also has hosted a fitness boot camp fundraiser and a wine tasting and conversation about FOMO–the fear of missing out–with a University of Chicago professor.

"The earlier we can bring in people to the cause and teach them about what BRF does and how it can make an impact, the more people get involved, the more people will donate moving forward," he said. Ben said he hopes the board's efforts will also help end the stigma associated with some disorders of the brain. He noted that his generation has a good track record of challenging the status quo and pushing back on stigma in many areas.

Ben said he's been impressed by the welcoming reception and support the YLB receives from BRF's Board of Trustees and leadership. This embrace of new ideas and new leaders is an outgrowth of the organization's commitment to taking the risks necessary to change the trajectory of brain research, empowering the next generation of innovators, and building momentum towards cures.

"They are trusting us to spread their mission to a new generation," he said.

Ben notes that his generation has a good track record of challenging the status quo and pushing back on stigma in many areas.

Like many families affected by neurological diseases, Ben and his family live with some uncertainty about what the future holds. There is currently no cure for Parkinson's disease. But they are focusing on enjoying their lives the way they are now. Ben recently moved to New York with PwC to continue his career in Deals Consulting. He said supporting BRF's efforts to build momentum in brain research towards developing new treatments gives him hope for the future.

"Finding a cure for others or helping move research in the right direction brings some comfort," he said.

[1]UN News. Nearly 1 in 6 of world's population suffer from neurological disorders – UN report. https://news.un.org/en story/2007/02/210312-nearly-1-6-worlds-population-suffer-neurological-disorders-un-report

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BRF recognizes the following individuals for their bequests, legacies and estate gifts:

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Olga Green
Mr. Dodge Teague, Jr.

In Honor

Mr. Ross Adams
Owen Anderson
Virginia & Norman Bobins
Mrs. Virginia Bobins
Mr. Norman Bobins
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Dr. Richard Chaifetz
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Molly Quinn
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Hope and Tom Reynolds
Durwood Robison
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Mr. Daniel P. Shapiro Family
Vincent Sherman
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Dr. Joanne Smith
Angeline Smith
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The Huggett Family
Alice Tucker
Mrs. Pamela Walgraeve
Ms. Carrie Walters
Mr. Jake Wendricks
Jerry White
Mr. Ethan Willbrand
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Marjorie Wortham

In Memory

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Ms. Beatriz Bergeron
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Aloha Poke
Antique Taco
Anything is Pawzible
Bark Box
Barry's Bootcamp
Beatrix
Binny's
Birchbox
Blowout Junkie
Blue Door Kitchen & Garden
Bon Vivant Cakes
Botanic Gardens
Breckenridge Grand Vacations
Brown Bag Seafood
Buena Vista Winery
Burlap & Barrel
CAMI NYC
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Carol's Cookies
Casper
CH Distillery
Chop Shop
Chopping Block
City Winery
Colectivo Coffee
Comfy Fitness
Coola
CorePower Yoga
Cross Town Fitness
Cupcakes & Cashmere
CycleX
Daily Harvest
DANNIJO
DIFF Eyeware
DineAmic Group
Dollar Shave Club
Dollop Coffee
East Bank Club
Eat Purely
Eberjey
Ema
Essie
Everlane
First Ascent
Five Point Holistic
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FloatSixty
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CHARITY NAVIGATOR
Four Star Charity

The Foundation's 4-star rating from Charity Navigator, the most well-respected nonprofit rating organization, gives our donors confidence that their funds are being used wisely. In fact, BRF earned a 100% rating in 2018 and 2019 for its accountability and transparency for adhering to best practices. Our efficiency and sterling track record for good stewardship allow us to make sure every dollar of every donation goes directly to research.

We do our best to accurately recognize all of our donors. If you see an error or omission, please contact us at 312.759.5157.

Letter from the Treasurer

Brain Research Foundation continues to fund ground breaking research thanks to the increasingly generous contributions of our donors and our superior investment performance. During the last two years, more than 100% of our annual donor contributions have been used to fund research and educational programs in neuroscience. We are proud of having achieved these results, on average, over the last nine years.

BRF continues to fund the most innovative neuroscience research in the most beneficial ways to advance the understanding of the brain. As we review all of our programs, we funded almost 2.9 million dollars of projects in the last 2 years. That amount exceeded our contributions by $140,000, thus meeting our objective of investing at least 100% of our annual support in worthy neuroscience programs. We are proud of our ability to be good stewards of our donor dollars.

We have included a summary of our income and major expenses and a condensed balance sheet for fiscal years 2018 and 2019. We encourage you to review our audited financial statements on our website or contact the BRF office.

The Board of Trustees and staff continue to work hard to sustain your support to fulfill our mission. As we start our 65th year, we look forward to building our donor base and funding more researchers who are focused on improving life through innovative neuroscience research.

Sincerely,

David H. Fishburn
Treasurer

Statement of Activities and Changes in Net Assets

Highlights of Income Statement year ended June 30, 2019 and 2018

		2019		2018
Beginning Net Assets	$	16,260,957	$	14,811,410
Contributions		1,584,524		1,155,391
Interest and Dividends		391,096		364,640
Net Realized and Unrealized Gains on Investments		790,950		1,750,294
Total	**$**	**19,027,527**	**$**	**18,081,735**
Expenses				
Program Services	$	1,400,389	$	1,479,280
Supporting Services		$280,134		341,498
Total	$	1,680,523	$	1,820,778
Total Net Assets	**$**	**17,347,004**	**$**	**16,260,957**

Statement of Financial Position

As of June 30, 2019 and 2018

Assets	2019	2018
Cash	$ 54,682	$ 40,965
Investments	17,660,767	16,612,428
Contributions Receivable	132,000	91,145
Prepaid Expenses and Other Current Assets	15,800	3,000
Security Deposits	5,200	5,200
Property and Equipment - Net	4,032	6,885
Total Assets	$ 17,872,481	$ 16,759,623

Liabilities and Net Assets	2019	2018
Liabilities		
Accounts Payable and Accrued Expenses	$ 33,771	$ 41,123
Deferred Rent Expense	21,706	27,543
Grants Payable	470,000	430,000
Total Liabilities	$ 525,477	$ 498,666
Net Assets		
Net Assets Without Donor Restrictions	$ 15,380,680	$ 14,244,675
Net Assets With Donor Restrictions	1,966,324	2,016,282
Total Net Assets	$ 17,347,004	$ 16,260,957
Total Liabilities and Net Assets	**$ 17,872,481**	**$ 16,759,623**

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