Discover

Winter 2021

News from Brain Research Foundation

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Beginnings

Dear Friends,

As I write this letter on the first month of the beginning of 2021, I reflect on a quote by Plato "The beginning is the most important part of the work." And I can't help but think about how important "beginnings" are to the mission of Brain Research Foundation.

We are dedicated to brain research from the very start—at the very beginning of a novel idea. Some of the greatest minds in neuroscience find themselves with an innovative idea, but need funding to move it forward. We fund their idea, and we let them take that idea and grow it into something brand new: a new outcome, a new direction, a new beginning.

In this newsletter you will see many beginnings. We will introduce you to a new board member, Gail Elden, who has already shown a wonderful passion for BRF and I thank her so much for taking an active role and sharing our message. We will also introduce you to our newest Scientific Review Committee member, Dr. Kerry Ressler from Harvard, who has already provided us with tremendous insight and expertise. You will also learn about our first virtual benefit which was very successful and included a panel discussion on autism. Additionally, we surpassed our benefit financial goal, something that was an extraordinary accomplishment during the pandemic.

And most importantly, we are at the beginning of one of the latest scientific feats – the COVID-19 vaccine rollout. Pfizer-BioNTech COVID-19 Vaccine showed 95.0% efficacy and Moderna COVID-19 Vaccine showed 94.1% at preventing COVID-19 illness, including its neurological issues. This is the beginning of the prevention of this virus and the many symptoms it causes, short and long-term.

As we continue to create new scientific beginnings together, I would like to thank our Board of Trustees, our Young Leadership Board, our sponsors and our friends for their extraordinary support in 2020. I hope that the beginning of 2021 is going well for you and your loved ones and thank you for your interest in Brain Research Foundation.

Warmly,

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

BRF welcomes Gail Elden to our Board of Trustees

Gail M. Elden is a seasoned clinical psychiatric social worker/therapist with over 25 years of practice. She was a clinical social work fellow in the Department of Psychiatry at Michael Reese Hospital, received her Master's Degree in Social Services from The University of Chicago and her Bachelor's Degree at Grinnell College. Gail is currently in private practice. Her areas of expertise include: self-psychology, treatment and crisis intervention. She offers aid in divorce, depression, vocational choices, grief counselling and coping with stress and anxiety.

The seeds of Gail's interest in the medical field were sown by her father, a physician. Interest in the mind was the foundation of Gail's career and her passion for brain research grew when her late husband Dick was diagnosed with melanoma which then spread to the brain.

BRF announces new Scientific Review Committee Member

Kerry Ressler, M.D., Ph.D.
James and Patricia Poitras Chair in Psychiatry
Chief, Division of Depression & Anxiety Disorders
Chief Scientific Officer, McLean Hospital
Professor of Psychiatry, Harvard Medical School

Kerry J. Ressler, MD, PhD, is the James and Patricia Poitras Chair in Psychiatry, and Chief of the Division of Depression and Anxiety Disorders at McLean Hospital, affiliate of the Harvard Medical School. He received his Bachelor of Science degree in molecular biology from M.I.T., and his M.D./Ph.D. from Harvard Medical School. In 1992 at Harvard, he was the first student of Dr. Linda Buck (Nobel Prize, 2004), helping to identify the molecular organization of the olfactory receptor system, and he has spent his career using molecular tools to understand systems neuroscience approaches to emotion and behavior.

Prior to moving to McLean in 2015, he spent 18 years at Emory University and Grady Memorial Hospital in Atlanta, where he founded the Grady Trauma Project, a study focused on understanding the Psychology, Biology, and Trauma-Related factors contributing to intergenerational cycles of trauma exposure and Posttraumatic Stress Disorder, Substance Abuse and Violence in over 12,000 participants from urban Atlanta. He continues to be active in this work as a visiting professor at Emory and through national leadership roles in understanding the biology and genetics of PTSD through large multisite consortia.

Dr. Ressler is a previous Investigator of the Howard Hughes Medical Institute and a current member of the National Academy of Medicine. He was also the 2017 President of the US Society for Biological Psychiatry, and currently serves on the Councils for the Society of Biological Psychiatry and the American College of Neuropsychopharmacology. His work focuses on translational research bridging molecular neurobiology in animal models with human genetic and epigenetic research on emotion, particularly fear and anxiety disorders. He has published over 400 manuscripts ranging from genetic basic molecular mechanisms of fear processing to understanding how emotion is encoded in the brain across animal models and human patients.

Brain Research Foundation's Scientific Review Committee (SRC) is made up of well-regarded researchers in the field of neuroscience. This committee lends its scientific expertise when reviewing the various research proposals submitted to the Foundation, evaluating proposals and making suggestions for funding.

The path to progress

Selected by our Scientific Review Committee and Board of Trustees, BRF's grantees advance neuroscience and the understanding of neurological diseases.

2020 Seed Grant Winners

Christian R. Burgess, Ph.D.
University of Michigan
Department of Molecular and Integrative Physiology

Project Title: Dopaminergic contributions to dexterous skill in cortex and striatum

Keywords: Dopamine; motor cortex; Parkinson's disease; striatum

Natalia V. De Marco Garcia, Ph.D.
Cornell University
Department of Neuroscience

Project Title: A circuit mechanism for the development of cortico-cortical connectivity

Keywords: Autism; development; neuronal circuits

Laura A. DeNardo, Ph.D.
University of California, Los Angeles
Department of Physiology

Project Title: Defining the role of early life experience in mPFC circuit assembly

Keywords: Development; stress; synapse

Sung Han, Ph.D.
Salk Institute for Biological Studies
Peptide Biology Laboratories

Project Title: The neural basis of opioid-induced respiratory depression

Keywords: Opioid receptor; opioid-induced respiratory depression

Anirvan Nandy, Ph.D. ➔
Yale University
Department of Neuroscience

The Serota Family Seed Grant

Project Title: A new paradigm for the neuroscience of navigation

Keywords: Autism spectrum; social anxiety; social behavior

Won Chan Oh, Ph.D.
University of Colorado
Department of Pharmacology

Project Title: Role of inhibitory synapses in shaping excitatory circuits

Keywords: Alzheimer's disease; excitatory and inhibitory synapses; Parkinson's disease; synaptic plasticity

Cody A. Siciliano, Ph.D.
Vanderbilt University
Department of Pharmacology

Project Title: Neural mechanisms of inferential learning

Key Words: Addiction; depression; inferential learning; imaging

Emily L. Sylwestrak, Ph.D. ➔
University of Oregon
Department of Biology

Women's Council Seed Grant

Project Title: Linking cell type to disease: mapping gene expression and neural activity in pathological reward processing

Keywords: Addiction; neural basis of behavior; opioids; rewards

Dr. Nandy's Project Summary:
How do social interactions dynamically shape the neural circuits of cognition? Maps of the physical and social environment (cognitive maps) in the brain have been theorized to be central to cognition. In highly social species like humans, cognitive computations frequently occur in social contexts. However, it remains unknown how social contexts shape cognitive maps. These studies will reveal specific neural mechanisms in the brain that underlie social navigation, paving the way to elucidate relevant neural dysfunctions in cognitive disorders such as social anxiety and autism spectrum disorder.

Dr. Sylwestrak's Project Summary:
Survival often hinges on learning how to avoid threats and how to obtain "rewards", such as food, water, and mating opportunity. The brain has evolved to quickly learn what actions lead to a reward, increasing the motivational drive to perform those actions and generating a perceived pleasure when obtaining the reward. The neural pathways that drive reward learning can be hijacked by drugs of abuse, often by acting on very specific cells. For example, morphine acts directly on only about 2% of neurons in the brain, but it has a devastatingly powerful effect on behavior in addiction. This research will help us understand how we could better target treatments to the most relevant cell types affected during addiction and withdrawal.

2021 Scientific Innovations Award Winners

Gregory Scherrer, Ph.D.
The University of North Carolina at Chapel Hill
Department of Cell Biology and Physiology

Project Title: Mechanisms of affective states and drug discovery at the intersection of chronic pain and opioid addiction

Keywords: Chronic pain; drug discovery; opioid addiction

Project Summary: Pain is normally a sensation that we experience when our body is exposed to damaging stimuli, such as the noxious heat of an open flame. However, when chronic, pain becomes a debilitating disease. In the absence of efficient alternative treatments, the use of opioids for pain management has increased dramatically in recent decades, driving an Opioid Epidemic, from which about 50,000 Americans die every year. A better understanding of the mechanisms underlying chronic pain is urgently needed to develop safer analgesics. Dr. Scherrer proposes a unique approach: to alter our brain's interpretation of peripheral pain signals in order to eliminate pain unpleasantness and restore patients' quality of life. His lab aims to discover drug targets that are present in the brain's neurons that generate pain unpleasantness but are absent from the reward and breathing neurons affected by opioids, with the goal of developing a completely novel and safer class of analgesics. If they succeed, the experience of chronic pain will be largely limited to sensations localized at the site of injury and would no longer be associated with debilitating negative emotions. **This research has the potential to end the Opioid Epidemic.**

Shigeki Watanabe, Ph.D.
Johns Hopkins University
Department of Cell Biology

Project Title: Intrinsic and extrinsic mechanisms underlying synaptic proteostasis

Keywords: Alzheimer's disease; neurodegenerative diseases; neuronal waste management; Parkinson's disease

Project Summary: Neurons are responsible for the rapid communication of signals throughout our brain and our body. They have exquisite structures that underlie their unique function. One such structure is the synapse, the location of signal transmission between two neurons. Unsurprisingly, synapse health is vital to neurons signaling. Synaptic proteins must be at specific locations to keep up with signaling demands. Yet compared to the life of a synapse, proteins have short lives and must be replaced when they are no longer functional. And with aging, defective proteins can accumulate at synapses, making the synapse dysfunctional. These defective proteins form aggregates - a common feature of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. Microglia, the brain's version of white blood cells, seem to engulf small regions of synapses containing aggregates and take a small bite out of the synapse. Thus, microglia may potentially be like synapse "garbage collectors" who take care of the synapse by removing the aggregates. **Understanding how the system works to remove defective proteins from synapses will likely contribute to future prevention or treatment of protein aggregation underlying many debilitating neurodegenerative diseases like Alzheimer's and Parkinson's disease.**

Ilana Witten, Ph.D.
Princeton University
Department of Psychology & Neuroscience

Project Title: A role for dopamine during rest and sleep in memory consolidation

Keywords: Alzheimer's disease; dopamine; rest; sleep; memory; memory disorders

Project Summary: One of the most fundamental functions of the nervous system is to form memories of salient experiences. Offline replay (for example, during rest and sleep) of neural activity after an experience may be important for creating a lasting memory. But how and why are certain experiences tagged for offline replay and permanent memory consolidation, while that vast majority are forgotten? Dr. Witten will examine the hypothesis that bursts of the neurotransmitter dopamine, released during neural replay, are critical for long-term memory storage. This hypothesis is motivated by previous work, which has established that dopamine is necessary for memory consolidation. However, where in the brain dopamine is required, and when and how it affects neural replay, remain unclear. This research addresses fundamental questions related to forming permanent memories, which could have clinical relevance for memory disorders, like Alzheimer's disease. **Ultimately, optical or electromagnetic deep brain stimulation could be used to boost dopamine-dependent consolidation and improve memory function in human patients.**

We carry on, virtually

While we were not able to gather in person for our annual Discovery Dinner this year, we were pleased to note that we had a record number of audience members. Mary and Scott Serota were the Chairs of the evening, and due to the extraordinary generosity of the Serota family, we were easily able to surpass our goal and raise almost $825,000. In addition, a wonderful friend close to the Foundation pledged a $50,000 anonymous match on the day of the event. Sincerest thanks to the Serota family, our anonymous donor, our dedicated trustees, sponsors and individual contributors, and everyone that joined us that evening.

One of the most challenging aspects (due to social distancing) was how to execute our annual fundraiser, the Discovery Dinner. Of course, we were not alone in this challenge, as many non-profits were faced with how to promote and fundraise during this pandemic. We are very fortunate that the main part of the Discovery Dinner is often an educational panel with experts in their field, surrounding various topics on neuroscience. Therefore, pivoting to a new format was not too difficult for us because we were easily able to convert from an in-person panel to a virtual one.

On Thursday, October 29th we hosted Autism Research: Genes to Behavior featuring three leading experts in autism research. The panel included the following:
Dr. Ted Abel, Iowa Neuroscience Institute, University of Iowa; **Dr. Edwin H. Cook, Jr.**, Department of Psychiatry, University of Illinois at Chicago; and **Dr. Suma Jacob**, Department of Psychiatry and Behavioral Sciences, University of Minnesota. The discussion was moderated by BRF's Executive Director and CEO, **Dr. Terre A. Constantine** and **Rob Johnson**, former board member and Emmy award winning journalist was our emcee for the evening.

Following is a brief excerpt of the panel discussion.

Dr. Constantine: What is autism spectrum disorder?
Dr. Cook: Autism spectrum disorder (ASD), which I'll call autism to make it easier, is a combination of two major problems. One is difficulty in social communication, and the other is restricted and repetitive behaviors. In social communication difficulties, an early example is when babies have lack of eye contact with their caregivers. An example of restricted and repetitive behaviors is when you see a younger child focused on a spinning wheel instead of playing with a toy truck in the usual way. Or when routines have to be followed or someone might get very upset.

Dr. Constantine: How are clinicians making a diagnosis?
Dr. Jacob: Clinicians look at the child's developmental history and also at current behavior. We have standardized behavioral tests as well as interviews where we can get detailed information about the different things like social communication and rigid inflexible or repetitive behaviors.

Dr. Constantine: What is the prevalence of autism?
Dr. Jacob: The current prevalence is 1 in 54. The Centers for Disease Control (CDC) have been updating this every handful of years.

Dr. Constantine: In 2000, the prevalence was 1 in 150. Why is it so much more prevalent now? Do we have an epidemic on our hands?
Dr. Jacob: We are better at diagnosis. And it is also more consistent because we've developed better tools to diagnose. So more children are being diagnosed early – and through school systems.
Dr. Abel: Another positive point of this I think is that the early diagnosis can help. It can help with access to therapies, treatments and

education that makes a difference in the lives of children in their development and in the lives of their families.

Dr. Constantine: What are the risk factors that we know today?
Dr. Jacob: There are genetic risk factors. In addition, there have been studies looking at parental age, early pre-term complications, low birth weight complications and maternal health. All those things that happen as a fetus/infant is developing can be involved and affect risk for autism.

Dr. Constantine: Is it true that there are over 100 genes that have been reported to be associated with autism? And what does that mean?
Dr. Cook: Yes that's true. These genes are affected by many individuals with autism having mutations in these genes not found in their parents. The number has increased greatly with the development of sequencing of the protein coding regions of genes on a large scale.

Dr. Constantine: And a lot of times when we start talking about genes and genetics we think that it means it's inherited. Is autism inherited?
Dr. Cook: About 50 to 90% of the risk for ASD is inherited. The paradox is those 100 genes I mentioned account only for about 10 to 20% of autism cases. Now those are genetic but not inherited because the parents didn't have them. So much of the risk that's inherited is polygenic, meaning that hundreds or thousands of subtle variations in genes contribute to both risk and protection from autism.

Dr. Constantine: Is there a way to determine who might have a higher risk of autism?
Dr. Cook: One interesting research development that we will watch over the next several years is something called a "polygenic risk score" in which one adds up all of those subtle risk factors to determine whether an individual carries more or less of this inherited risk.
Dr. Abel: Sleep may play a part. You could look with a survey at sleep differences and difficulties in individuals with autism and see how that was connected to this polygenic risk score.

Dr. Constantine: Are there treatments for autism?
Dr. Abel: There's no silver bullet that can fix autism. But there are treatments like cognitive behavioral therapy and behavioral management therapy. Those treatments are often in coordination with school and often begin in pre-kindergarten and kindergarten. And individuals with autism often have other medical challenges and issues. So broad medical management of other challenges, like issues with their GI tract or asthma or other issues that can affect their performance. But ongoing therapy even into adulthood of speech and language and occupational therapy continues to be important.

Dr. Constantine: Where do you think the biggest breakthrough in autism research is going to come from?
Dr. Cook: Almost 30 years ago when BRF was funding pilot awards, people were asking, "Why would you study genetics and autism? You're not going to get anywhere." And now we have over 100 genes that are associated with it. We are in the midst of figuring out what all these genes do. That's the critical next step.
Dr. Abel: I would add that we need to know more about development. Autism has its basis in development and that basis might even be prenatally as well. Because you have a baby that is developing differently and gets diagnosed at 2 ½ - 3 ½ half years of age with autism but the origins of that go back in development. And that is the real challenge.

Dr. Constantine: Early intervention is key and helps a lot. Will new treatments that researchers identify help adults with autism?
Dr. Cook: The short answer is we don't know. However, in my clinic, I have a patient I have followed for 30 years and we found out he had a mutation in a gene associated with autism – SYNGAP1. Working with another basic laboratory, we treated my patient, who is in his 30s, with a drug and are seeing benefits. The patient is more curious and learning to do new things. It's a subtle effect but it is an effect. I think the first thing we have to think about is making people's lives with autism more comfortable, helping people with their adaptation.

Dr. Constantine: I have one final question. Do vaccines cause autism?
Dr. Abel: No. They do not. There's no evidence to support that. In fact, the evidence that was published was found to be incorrect and fraudulent from a Dr. Wakefield in the United Kingdom. So the answer is a resounding no.

If you would like to view this discussion in its entirety, please go to our Brain Research Foundation YouTube Channel (www.youtube.com/user/brainfoundation).

In 2020, the CDC reported that approximately 1 in 54 children in the U.S. is diagnosed with an autism spectrum disorder.

There are over 100 genes that have been reported to be associated with autism.

Boys are four times more likely to be diagnosed with autism than girls.

Early interventions may improve cognitive ability, social behavior, communication and daily living skills.

There is no evidence that vaccinations cause autism.

Source: www.cdc.gov

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The Brain and COVID-19

By now you have heard of the many possible neurological effects of COVID-19 including loss of smell, inability to taste, seizures, and stroke.

Although the mechanisms are not fully understood, there is an emerging consensus that smell loss occurs when the corona virus infects cells that support neurons in the nose. Some people have not recovered their sense of smell, and for a portion of people who have, odors are now distorted.

Other potentially devastating neurological symptoms such as stroke, brain hemorrhage and memory loss are not necessarily unheard of in other serious diseases, but the scale of those affected in the COVID-19 pandemic means that tens of thousands of people could have these symptoms, and for some, these might be lifelong problems.

Less common complications include peripheral nerve damage, typical of Guillain–Barré syndrome, anxiety and post-traumatic stress disorder.

What is incredible about Brain Research Foundation is that we have a long history of research in all these areas. This is what makes our Foundation so unique, our commitment to investigating ALL brain disorders and conditions, because the brain is complex and interconnected.

All of us at BRF stand firm in the belief that the more we know about the brain: how it works, what causes damage and how it heals, the quicker scientists can apply their knowledge to these potentially debilitating neurological issues. This knowledge is helping doctors today and will also help them in the future.

When you donate to Brain Research Foundation, you are helping scientists learn how to best protect the brain from inflammation, viruses, neurodegeneration, cancer or trauma. And the more they know now, the quicker they can present a path to healing.

Source: www.nature.com