THE KLARMAN FAMILY FOUNDATION

Eating Disorders Research Grants Program
2017 Grant Cycle

Grant Recipients

Three-Year Grants

Mark Andermann, Ph.D.
Beth Israel Deaconess Medical Center

"Focus on the positive: pathways for biasing responses to mixed-valence food cues"

Fasting increases positive reactions to food signals, and decreases defensive reactions to danger signals that inhibit food-seeking. Patients with anorexia nervosa (AN) exhibit a selective behavioral bias to danger signals, and an associated neural response bias insular cortex, an area essential for food-seeking under threat. We hypothesize that habitual fasting in AN patients serves to partially attenuate the flow of anxiety-promoting signals to the basolateral amygdala (BLA), and that the behavioral and insular cortex hypersensitivity to danger signals in AN is mediated by excessive flow of anxiety-promoting signals from the paraventricular thalamus (PVT) to BLA, thereby modifying the perceived valence and salience of learned cues. To test this hypothesis, we will use a new method to repeatedly image the activity of hundreds of identified neurons in the insular cortex of healthy and AN model mice exposed to visual food cues, danger cues, or mixed cues, combined with specific manipulations of the pathway from PVT to BLA. We will then test whether the excessive behavioral and neural responses to danger cues in AN mouse model can be rescued by directly tamping down the pathway from PVT to BLA, thereby providing a sensitive framework for development of pathway-specific therapies.

Scott Crow, M.D.
University of Minnesota

"Goal based learning and habit in Anorexia Nervosa"

Anorexia Nervosa (AN) symptoms are difficult to treat and often last for years or even decades. This may be because they serve a purpose by making people feel better or helping to eliminate bad feelings (goal directed learning), or because overtime they become ingrained and second-nature (habit learning). This study will follow people with AN for 12 months. At the beginning, goal directed and habit learning will be measured using brain scans and questions that people

answer on their cell phones. We predict that evidence of goal directed learning will be stronger in people whose AN has recently started and evidence of habit learning will be stronger in people who have had AN longer. We also predict that evidence of habit learning will predict having more eating disorder problems after 12 months. Understanding the how the brain makes decisions at different time points during AN can help us to develop better treatments that will be well suited to different stages of illness.

Daphna Shohamy, Ph.D.
Columbia University

"Mechanisms of decision-making in Anorexia Nervosa: a computational psychiatry approach"

Anorexia Nervosa is a devastating illness with substantial morbidity and a mortality rate among the highest of any psychiatric illness, characterized by persistent, rigid dietary restriction leading to low body weight and complications of starvation. We propose to examine the cognitive and neural mechanisms that contribute to choice of foods in patients with Anorexia Nervosa, using state-of-the-art tools and computational modeling, to determine whether and how these processes differ from healthy controls, what the underlying brain differences are, and whether and how behavioral training can modify choice. Our study will develop a new pathway for understanding and treating the salient behavior of restrictive eating that contributes to the significant disease burden of Anorexia Nervosa.

Kellie Tamashiro, Ph.D. and Angela Guarda, M.D.
Johns Hopkins School of Medicine

"Neural Mechanisms of Appetite Dysregulation in Anorexia Nervosa: The Role of AGRP"

Anorexia Nervosa (AN) is a severe eating disorder for which there is no effective treatment. AgRP is a brain neuropeptide that increases appetite and is involved in addiction, anxiety-related behaviors and response to stress. Individual differences in AgRP and its brain circuits may explain why some patients develop severe and enduring AN and others recover. The rodent model of AN known as "activity-based anorexia" (ABA) results in self-starvation, excessive exercise and weight loss. Our preliminary data found that a subset of ABA animals (those with a passive coping style and exposed to early life stress) had lower AgRP levels and lost more weight. This proposal examines AgRP in adult inpatients with AN before and after weight gain. We will measure blood levels of AgRP and their relationship to brain imaging in women with AN compared to healthy women. Results will provide new information about brain changes in AN and how these predict differing weight restoration trajectories and treatment response. This information could help clinicians identify what therapy will be most effective for which patients. Furthermore, results could identify novel targets in the brain that may help develop more effective medications or treatment interventions for AN and related eating disorders.

Lori Zeltser, Ph.D.
Columbia University

"Stress and Eating Behavior in Anorexia Nervosa"

Structured inpatient behavioral treatment programs can increase food intake and restore body weight in individuals with anorexia nervosa (AN), but there is a very high rate of relapse. The Eating Disorders Research Unit at the New York State Psychiatric Institute has used objective measurements in laboratory-based meal tests to assess eating behaviors in AN. We demonstrated that there is a strong link between anxiety and the avoidance of high calorie foods, even after body weight restoration. Moreover, consumption of a lower fraction of calories from fat at discharge is associated with poor outcomes one year later. Since anti-anxiety medication fails to impact anxiety or food intake in AN, there is a need to identify new therapeutic targets. The Zeltser lab at Columbia University has developed a mouse model to study how social stress and dieting can lead to anorexia-like behavior in genetically-susceptible individuals. We used this model to identify a novel target for AN treatment. The proposed studies will validate assays to evaluate the relationship between anxiety and avoidance of fattening foods in mice and human subjects and thereby provide a critical foundation to assess the potential clinical utility of candidate pharmaceutical compounds in AN.

One-Year Pilot Studies

Scott Bunce, Ph.D. and Fauzia Mahr, M.D.
Pennsylvania State University

"Evaluating the Role of the Bed Nucleus of the Stria Terminalis in the Neurocircuitry of Anxiety in Patients with Anorexia Nervosa Restricting Type"

Anxiety contributes to the development and maintenance of anorexia nervosa (AN) symptoms, and high trait anxiety and anxiety disorders are common in AN patients. A very small nucleus, the bed nucleus of stria terminalis (BNST), plays a critical role in organizing how we respond to anxiety-producing (versus acute fear) situations. Elevated resting BNST metabolism mediates anxious temperament in primates. The BNST is also smaller in females, and, in animal models, this change occurs around or after puberty through cell death in females and cell growth in males. However, no studies have reported examining the structure or function of BNST in AN. In this study, we use a novel form of a well-known neuroimaging technique (fMRI) to image both size and function of BNST while participants engage in an anxiety-eliciting task. Uncertain, versus certain, expectation of seeing unpleasant images is expected to elicit greater BNST activation in both AN and high anxiety adolescent females relative to healthy controls. When the task "threat" is changed to the receipt of a sweet taste, we expect differential BNST activations in AN relative

to both high anxiety and healthy control groups. This research is expected to help design new treatment targets for patients with AN.

Jeffrey Friedman, M.D., Ph.D.
Rockefeller University

"Dissecting a Septal Circuit Involved in the Crosstalk between Stress, Anxiety and Anorexia"

Anorexia Nervosa (AN) is a clinically important syndrome that tends to affect young women and that is characterized by restrictive eating. The National Association of Anorexia Nervosa and Associated Disorders (ANAD) estimates that 0.9% of American women suffer from AN in their lifetime and 25% of deaths from AN patients are from suicide. About half of patients with AN also present depression and anxiety as a common comorbidity. However, it remains unclear how these psychiatric alterations influence the neurobiology of AN. Neurotensin is a peptide that regulates mood by interacting with the dopaminergic system in mammals and its levels in plasma are altered in patients with affective disorders.

We propose that neurotensin plays a role in the neurobiology of AN by providing a biological link between mood alterations and restrictive eating. By using state-of-art techniques in imaging, neuroscience and behavioral science we will identify the neural circuitry involved in the cross talk between anxiety and restrictive eating and further manipulate these circuits in order to prevent AN symptoms. Our proposal will provide a novel target for treatments for AN and will shed light on the biology underlying AN comorbidities.

Joel E. Kleinman, M.D.
Johns Hopkins University

"Molecular Biology of Anorexia Nervosa"

Anorexia nervosa (AN) is a complex psychiatric and human brain disorder with a high rate of morbidity and mortality. Current treatment options thus far have mixed success in achieving remission in AN. In order to understand the underpinnings of AN, our lab has a long-term objective to elucidate the molecular biology of AN with the goal of identifying potential novel targets for treatment. Two specific aims are required to achieve this goal. First, is to determine the molecular biological mechanism of the genetic risk. Second, is to determine if that mechanism is abnormal in the brains of patients with AN/ED. This will be accomplished with molecular biological methods (RNA sequencing and genotyping) routinely used at Lieber Institute for Brain Development (LIBD) and applied to a unique collection of AN/ED brains and controls collected and characterized by LIBD.

Carrie J. McAdams, M.D., Ph.D.
University of Texas Southwestern Medical Center

"Biological Factors Related to Treatment-Refractory Anorexia Nervosa"

Anorexia nervosa is defined as a mental illness because many of its symptoms include cognitive distortions and behavioral changes related to feeding. However, in healthy people, physiological changes, such as occur during physical illness, also systematically alter cognitive perception and behaviors. We have identified differences in brain activations in anorexia nervosa related to course of disease, by comparing recently-ill women to long-term recovered women; interestingly, these differences are in the same brain regions that change during physical illness. Anorexia nervosa involves severe physical changes, which include elevated levels of inflammation and changes to the types of symbiotic bacteria that inhabit the gastrointestinal track. This proposal will examine whether physiological changes related to inflammation correlate with neural activations in women with anorexia nervosa, by simultaneously measuring brain function, levels of inflammation in the blood and types of bacteria in the gut. Second, this pilot study will recruit subjects in two specialized cohorts: those in sustained weight-recovery following anorexia nervosa and those that have been treatment-refractory. These two groups will be compared to determine if factors related to inflammation perpetuate the disease by changing the brain to alter cognition and behaviors.

Carol B Peterson, Ph.D.
University of Minnesota

"Investigating the Impact of Oxytocin on the Neurobiological Underpinnings of Socioemotional Deficits in Anorexia Nervosa"

This investigation will examine how oxytocin (OT), a hormone that impacts social behavior, can change the brain functioning of individuals with anorexia nervosa (AN). Brain scans of adults with AN will be compared to brain scans of individuals without AN after receiving OT (nasal spray) and viewing pictures of faces with different emotions and completing a task related to social acceptance and rejection. Study participants will also eat a test meal after receiving OT to examine the impact on eating behavior. Brain scans and eating behaviors of individuals with AN who receive OT will also be compared with scans of the same individuals who, on a different day, receive saline. These comparisons will determine whether brain changes and eating behaviors are directly related to the OT rather than "placebo". This study will provide important information about how OT changes the brain functioning and eating behaviors of individuals with AN. Given the importance of social perception in AN, OT may provide a powerful method of changing brain regions associated with social relationships as well as increasing food intake among individuals with AN.