Short-Term Research Objective 1.C.
Identify cognitive dysfunction/neural circuitry profiles (e.g., anhedonia, impaired executive functioning) associated with suicide risk that may be amenable to current interventions.

Funding Organization: American Foundation for Suicide Prevention
Study Title: White Matter Integrity and Suicide Risk: Histologic Evaluations of Potential DTI Targets
Principal Investigator: Andrew Dwork
Year When Study First Received Funding: 2008
Abstract: Our goal is to study autopsy brains in order to localize abnormalities that could be identified on magnetic resonance imaging (MRI) of live patients to assess suicide risk. We will use uniform random sampling to conduct histological analyses of myelin integrity and microglial activation in frontal white matter from autopsy brains that we have already collected from 27 suicide cases and 27 nonsuicide cases matched for diagnosis, age, sex, and medication history. The data will allow us to identify and to localize subtle variations in white matter integrity that may be associated with suicide. We will also examine whether such abnormalities are associated with a history of aggressiveness or violent behavior, characteristics that have been associated with suicide and that may be associated with abnormalities in prefrontal white matter. White matter abnormalities can be recognized in live subjects with high sensitivity by diffusion weighted MRI and magnetization transfer MRI. Finding a white matter abnormality that is associated with suicide could allow the use of MRI to help assess suicide risk in individuals, so that close observation and other intense preventive efforts could be directed towards those individuals for whom they are most needed.

Funding Organization: American Foundation for Suicide Prevention
Study Title: Cognitive and Biological Responses to Social Stimuli as Longitudinal Predictors of Adolescent Girls’ Suicidality
Principal Investigator: Mitchell Prinstein
Year When Study First Received Funding: 2008
Abstract: To understand how specific biological and social-cognitive responses to interpersonal stress may be associated with a greater likelihood of future suicidal ideation and behavior among adolescent girls. This study offers a rare opportunity to examine adolescent girls' responses to interpersonal stimuli using a lab-based, experimental paradigm, and a longitudinal design. Adolescent girls will be asked to participate in an established interpersonal stressor during a videotaped lab-based visit, and to complete measures of suicidality at four time points (baseline, 3, 6, and 9 months later). Measures of HPA Axis functioning and vagal tone SUPPRESSION will be obtained to measure biological responses, and videotapes will be analyzed and coded to measure social-cognitive responses. Past research has identified stressor domains (i.e., school, family, peers) associated with suicidality, but little research has addressed how or why these stressors lead to adolescents' decisions to engage in suicidal behavior. By examining both social-cognitive and biological responses to interpersonal stimuli, this study offers an integrative model with direct implications for preventive interventions; it will be possible to more accurately identify adolescents at risk and to modify processes that mediate the link between stressful events and suicidal behavior.
**Funding Organization:** American Foundation for Suicide Prevention  
**Study Title:** Measuring Suicidality in Adolescent Major Depressive Disorder Using fMRI  
**Principal Investigator:** Michael Stevens  
**Year When Study First Received Funding:** 2008  
**Abstract:** The aim of this study is to use functional magnetic resonance imaging (fMRI) to describe differences in emotion-related neural activity between sub-groups of previously suicidal depressed adolescents who have different profiles of suicide attempt histories in order to replicate and extend previous adult results. The study will involve recruitment, standardized psychiatric evaluation, and fMRI assessment of 30 adolescents ages (12-19) with Major Depressive Disorder and history of suicide and a demographically matched control group of 15 healthy teens. The MDD sample will be split evenly between those who have a history of impulsive suicide behavior and those who do not. We will compare groups on brain activity elicited by an emotion provocation paradigm that measures the function of neural systems which are theoretically relevant to MDD and known to function abnormally in MDD adults. This will be the first fMRI study to examine brain activity in suicidal teenagers. The findings will greatly increase our understanding of how differences in brain function may confer risk for specific types of suicidal behavior.

**Funding Organization:** American Foundation for Suicide Prevention  
**Study Title:** Cognitive Correlates of Suicidality in Late-life Depression: Identifying Targets for Prevention and Treatment  
**Principal Investigator:** Katalin Szanto  
**Year When Study First Received Funding:** 2008  
**Abstract:** In the proposed study we aim to explore what makes elderly, who have the highest suicide rate in the U.S., vulnerable to suicidal behavior. More specifically we will explore the thinking patterns of suicidal elderly. Based on existing literature and our own observations, we believe that suicidal elderly may be impaired in three domains of thinking: problem solving, decision making, and abilities needed for social interaction. We will study these in two groups of elderly - 60 suicidal depressed patients (who recently attempted suicide) and 60 depressed non-suicidal patients (no lifetime history of suicidal ideation or attempt). The study will involve specific neuropsychiatric and clinical evaluations in addition to comprehensive psychiatric, physical, and suicide assessments. The need for targeting suicidal behavior in this high risk group is highlighted, not only by the high rate of such behavior among this population, but also by the fact that in our previous study we found that suicidal depressed elderly had significantly lower treatment response rates than non-suicidal ones and needed twice as long time to get well even when they received state-of-art antidepressant treatment and interpersonal psychotherapy. Understanding specific abnormalities in thought patterns of suicidal elderly could facilitate better assessment and identification of vulnerable elderly and will help create new psychotherapeutic treatments.
Funding Organization: American Foundation for Suicide Prevention
Study Title: Neurobiology of Inhibitory Control in Late-life Suicide
Principal Investigator: Alexandre Dombrovski
Year When Study First Received Funding: 2009
Abstract: Suicide attempts are far more likely to result in death in the elderly than in younger people; a suicide attempt follows a decision which the rest of us see as unfortunate, and recent studies indicate flaws in suicide attempters' decision-making; using brain imaging, we will try to understand whether elderly with depression who have attempted suicide are impaired in their ability to use brain circuits involved in making decisions compared to similarly depressed elderly without past suicide attempts. After a careful assessment of their mental health and medical history, past suicidal behavior, and cognition, 40 elderly depressed participants (20 with past suicide attempts and 20 without past attempts or suicidal ideation) will undergo a non-invasive brain scan (functional magnetic resonance imaging, fMRI) as they make decisions guided by positive or negative feedback. We will examine whether elderly with past suicide attempts fail to flexibly adjust their decision-making and show altered activity of the brain circuit that is critical to decision-making (ventral prefrontal-striatal circuit). The two comparison groups will be similar on the severity of depression, burden of physical illness, and global cognitive impairment. Decision-making is not currently explicitly addressed by any psychotherapy or medication regimen for treating suicidal elderly, though some medications currently used in depression and Parkinson's disease affect neurotransmitter systems (e.g., dopamine and serotonin) involved in decision-making. This study could suggest not only the importance of decision-making mechanisms but what specific brain circuits to target in the development of new interventions for older people at risk for suicide.

Funding Organization: American Foundation for Suicide Prevention
Study Title: Childhood Traumatic Stress and Adolescent Girls’ Suicidality: A Longitudinal Examination of Psychophysiological Mechanisms
Principal Investigator: Nicole Heilbron
Year When Study First Received Funding: 2009
Abstract: The primary aim of this study is to examine how the psychobiological effects of childhood trauma may be associated with an increased risk of suicidality among adolescent girls. The proposed study offers an innovative methodology to examine physiological mechanisms believed to underlie associations between childhood trauma and suicidality. Measures of (1) fear-potentiated startle reactivity, a psychophysiological measure of fear reactivity, and (2) prepulse inhibition of startle (PPI), a psychophysiological index of information processing, will be analyzed to examine stress reactivity and neurocognitive functioning. Participants will complete measures of childhood maltreatment, traumatic stress, and suicidality at the baseline assessment and at two additional time points (3 and 6 months later). Although childhood trauma has been established as a robust predictor of suicidal ideation and suicide attempts, relatively few studies have explored how physiological adaptations to childhood traumatic stress may be related to adolescent suicidal behaviors. This longitudinal study will inform suicide prevention efforts by examining biological pathways between childhood trauma and suicidality, thus contributing to knowledge of suicide risk factors and highlighting possible targets for future prevention and intervention programs.
**Funding Organization:** American Foundation for Suicide Prevention  
**Study Title:** Bio-behavioral Markers of Affect Regulation in Teen Suicide Attempters vs. Non-suicidal Self-injurers  
**Principal Investigator:** Daniel Dickstein  
**Year When Study First Received Funding:** 2009  
**Abstract:** The goal of our study is to identify how adolescents who have attempted suicide differ from those who engage in non-suicidal self-injury (such as cutting themselves) with respect to how they handle their emotions. We will study three groups of teens (ages 13-17 years): (1) teens who have attempted suicide 2 or more times, but who do not engage in non-suicidal self-injury (cutting), (2) teens who cut/self-injure, but who have not attempted suicide, and (3) typically-developing teens without psychiatric illness. The reason to study multiple suicide attempters (MSAs) is because they are a more homogeneous, uniform group who are more likely to engage in future suicidal behavior compared to first-time attempters (Esposito 2003). To identify bio-behavioral markers that separate teen suicide attempters from those who cut themselves, we will measure: (a) psychological factors (including self- and parent ratings of suicidality and non-suicidal self-injury, psychiatric disorders and early life trauma/neglect, behavior problems including aggression, and substance use) and (b) performance on computerized behavioral games (including identification of facial emotions, cognitive function (e.g., decision-making, attention, executive function), response to interpersonal collaboration and conflict, and associations between oneself and suicidality). While many have theorized that problems of affect regulation underlie both teen suicide attempts and nonsuicidal self-injury (cutting), our study will be the first to objectively test these theories by using psychological assessments and computerized behavioral tasks, each tapping into an aspect of affect regulation, to identify bio-behavioral markers of teen suicide and cutting. Such bio-behavioral markers of teen suicide and cutting identified by our study will contribute to suicide prevention by (1) improving what is known about the underlying neurobiology of teen suicide and cutting, and (2) providing critical preliminary data for future functional magnetic resonance imaging studies of teen suicide and self-cutting, and (3) resulting in improved identification and treatment of teens at risk for suicidal behavior by using such bio-behavioral markers to augment clinical history in the psychiatric care of teens, and thus in the future to prevent teen suicides.

**Funding Organization:** American Foundation for Suicide Prevention  
**Study Title:** Diffusion Tensor Imaging (DTI) Studies of Suicidal Behavior  
**Principal Investigator:** Emil Coccaro  
**Year When Study First Received Funding:** 2009  
**Abstract:** The key aim of this study is to examine the structural integrity of white matter tracts in the brains of individuals who have a history of attempting suicide. Individuals with Borderline Personality Disorder (BPD) with and without a history of suicide attempts will be compared to healthy controls with Diffusion Tensor Imaging (DTI). This form of neuroimaging examines the integrity of white matter tracts and localizes differences in the integrity of white matter tracts among comparison groups. Demonstration of abnormalities in white matter tracts in individuals with histories of suicide attempts will highlight the role played by white matter integrity, as well as the nature of the neuronal circuits, that may be involved in suicide risk. Such work will enhance our understanding of neuronal pathways in individuals with histories of suicidal behavior.
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**Funding Organization:** American Foundation for Suicide Prevention  
**Study Title:** Dysfunction of Prefrontal Cortex, Cognitive Control and Suicide Risk in Schizophrenia  
**Principal Investigator:** Michael Minzenberg  
**Year When Study First Received Funding:** 2010  
**Abstract:** The aim of this study is to determine if problems with a part of the brain called the prefrontal cortex, and associated inability to control one’s behavior (called cognitive control), is a determinant of suicide risk in patients with schizophrenia. This study will involve testing patients who are in the first year of schizophrenia with functional magnetic resonance imaging (fMRI) while they perform a task that measures cognitive control. We will also evaluate these patients with clinical measures of suicide risk, depression, impulsivity, and the characteristic symptoms of schizophrenia. We predict that these patients will show impaired activity in the frontal cortex of the brain, and related problems in the control of their behavior, which will be associated with the degree of suicide risk. The brain dysfunction that underlies the elevated suicide risk in schizophrenia patients remains uncertain, despite a wealth of knowledge concerning neural and psychological disturbances in this illness. Identification of how brain dysfunction relates to elevated suicide risk will be critical to the development of new treatments to minimize this risk.

**Funding Organization:** American Foundation for Suicide Prevention  
**Study Title:** Cognitive Control and Emotion Processing Markers of High-Intent Suicide Ideations in Adolescents  
**Principal Investigator:** Fadi Maalouf  
**Year When Study First Received Funding:** 2010  
**Abstract:** This study aims at investigating cognitive control of emotion processing, an important aspect of emotion regulation, in adolescents with high-intent suicide ideation as compared to non-suicidal and healthy adolescents using computerized behavioral tasks and self-report measures. We propose to recruit 30 adolescents with major depressive disorder and high-intent suicide ideation (defined as suicide ideation with a plan within the year preceding the assessment), 30 adolescents with no history of suicide ideation and 30 healthy controls. Subjects will be interviewed, given self-reports and administered computerized behavioral tasks to assess various aspects of cognitive control, emotion processing and the interface of the two. We aim at comparing performance of the three groups on these tasks and investigating whether they predict worsening of suicidal ideation or suicide attempt at a nine-month follow-up. This will be the first study to examine the cognitive and emotion processing profile in young high-intent suicide ideators and how it longitudinally predicts suicide attempts. The cognitive and emotion processing deficits, once identified in this population, may be targeted by future interventions to help prevent the potentially fatal outcome of a suicide attempt.

**Funding Organization:** American Foundation for Suicide Prevention  
**Study Title:** An fMRI Study of Affect Arousal and Cognitive Control in Suicidal Subjects with Borderline Personality Disorder  
**Principal Investigator:** Paul Soloff  
**Year When Study First Received Funding:** 2010  
**Abstract:** Suicidal patients are characterized by deficits in emotion regulation and executive cognitive function, increased vulnerability for impulsive and aggressive behaviors, structural and metabolic brain abnormalities in
areas of prefrontal cortex. These deficits appear highly interrelated and may constitute a neurobiological diathesis to suicidal behavior independent of diagnoses. This study will use functional Magnetic Resonance Imaging (fMRI) in subjects with borderline personality disorder and histories of medically significant suicide attempts to define the neural basis by which affective arousal impairs executive cognitive functions and contributes to impulsive suicidal behavior. Twenty female borderline personality disorder subjects, 10 attempters and 10 non-attempters, will be compared to 10 control subjects on three fMRI cognitive performance tasks, each incorporating emotional stimuli (positive, negative or neutral faces or pictures). The cognitive tasks engage the function of brain regions previously shown to be structurally or metabolically abnormal in borderline personality disorder. We will assess the degree to which affective arousal impairs cognitive task performance, and compare patterns of neural activation reflecting excitation and inhibition in suicidal and non-suicidal borderline personality disorder subjects with healthy control subjects. This study will characterize the neurobiological basis of the borderline patient’s failure of inhibitory control over emotion and behavior at times of affective stress and contrast subjects with medically significant suicide attempts with non-attempters and control subjects. Identification of dysfunctional brain networks using readily available fMRI techniques may provide a biological marker for patients at highest risk for impulsive suicidal.

Funding Organization: American Foundation for Suicide Prevention
Study Title: Alcohol as an Acute Risk Factor for Suicide Attempts: A Case-crossover Pilot Study
Principal Investigator: Courtney Bagge
Year When Study First Received Funding: 2011
Abstract: Given the clinical and public health significance of suicide, there is considerable interest in identifying acute factors that increase the risk for suicide attempts. As such, the aim of the current research is to characterize the role of acute alcohol use within suicide attempts. It is well recognized that drinking often surrounds suicide attempts; approximately 40% of adult suicide attempters ingest alcohol prior to their attempt. However, the majority of research on drinking and suicide is descriptive in nature, and, thus, cannot speak to their relation. The aim of this study is to determine whether suicide attempters are more likely to drink on the day of their attempt compared to a day when they did not attempt suicide, taking into account other factors that vary from day-to-day. Eighty individuals presenting for medical evaluation after a suicide attempt will complete a battery of questionnaires and interviews assessing participants’ experiences, substance use, and mood during the 48 hours prior to their suicide attempt. Analysis of this data will test the unique role of proximal alcohol use in suicide attempts. It is anticipated that the pilot study’s results will help fill an important gap in our knowledge and inform suicide prevention efforts.

Funding Organization: American Foundation for Suicide Prevention
Study Title: Neural Substrates of Emotion Dysregulation and Self-harm in Suicide Attempters
Principal Investigator: Michael McCloskey
Year When Study First Received Funding: 2011
Abstract: The study will investigate fMRI signals from borderline personality disorder females who will engage in tasks during the MRI designed to elicit emotional responses relating to self-aggression and suicidal behavior. This work will provide the brain circuitry associated with the failure to regulate negative emotions and the initiation of self-harming behavior in a group of previously suicidal women with borderline personality disorder. While undergoing the fMRI scan the individuals will be subjected to emotionally evocative pictures.
and a stimulus emulating self-harm. The difference between suicidal and non-suicidal subjects in the limbic and cortical areas of brain activation will be compared to identify patterns of brain activation associated with suicide risk. This is an important investigation targeting core issues of the neurobiology of suicide. No one has done this before, thus highly innovative.

**Funding Organization:** American Foundation for Suicide Prevention  
**Study Title:** A Functional Magnetic Imaging Study in First-degree Relatives of Suicide Complete  
**Principal Investigator:** Fabrice Jollant  
**Year When Study First Received Funding:** 2011  
**Abstract:** Studying the family members of individuals who died by suicide helps us understand more about genetic vulnerability for risk factors for suicide by comparing them with individuals with a family history of depression and no suicide and those with no family history of either depression or suicide. Dr. Jollant will use the brain imaging technique known as fMRI to discover whether cognitive and emotional vulnerability traits are shared within families. During brain imaging, participants will be asked to respond to faces expressing various emotions including anger, sadness, and happiness, and they will also perform the Iowa Gambling Task that measures an individual’s thinking flexibility and impulse control. Dr. Jollant expects that family members of those who died by suicide will perform differently on these two tasks and evidence differences in brain function.

**Funding Organization:** American Foundation for Suicide Prevention  
**Study Title:** Objective Sleep and Suicide in General Population Sample of Youth  
**Principal Investigator:** Ravi Singareddy  
**Year When Study First Received Funding:** 2011  
**Abstract:** Substantial evidence indicates that sleep disturbances such as insomnia, hypersomnia, and nightmares increase the risk of suicidal behaviors. Dr. Singareddy aims to determine the association among suicidal ideation, suicidal attempts and sleep disturbances in 500 adolescents. He will record specific aspects of sleep in a sleep laboratory, including sleep efficiency, sleep latency, REM latency, poor subjective sleep, nightmares, and hypersomnia or oversleeping. He hypothesizes that adolescents experiencing suicidal ideation or history of a suicide attempt will also be suffering from measurable sleep problems. Further, he expects the severity of suicidal ideation to increase when sleep disturbances are accompanied by difficulties in attention and concentration, impulsiveness, and increased risk-taking behaviors.

**Funding Organization:** American Foundation for Suicide Prevention  
**Study Title:** The Neural Circuitry of Suicidality in Adolescent Depression  
**Principal Investigator:** Hilary Blumberg  
**Year When Study First Received Funding:** 2011  
**Abstract:** Dr. Blumberg will use a brain scanning technique known as functional magnetic resonance imaging (fMRI) to identify differences between the brain circuitry of depressed adolescents who have made a suicide attempt and depressed adolescents who have not attempted suicide. Both groups will be asked to perform certain tasks while brain images are taken. In addition, the adolescents will complete an interview, perform behavioral tasks, and complete questionnaires relating to suicidal ideation and behavior, aggression, and
impulsiveness. Dr. Blumberg will also measure the density of brain fibers, known as white matter. She is testing the hypothesis that adolescents with major depression and a history of suicide attempts show a decrease in regulation and structural integrity of the brain circuitry of the frontal cortex, the part of the brain responsible for emotion and impulse control.

**Funding Organization:** American Foundation for Suicide Prevention  
**Study Title:** Fatal Decisions: Behavioral Economic Study of Decision Pathways to Suicidal Behavior  
**Principal Investigator:** Katalin Szanto  
**Year When Study First Received Funding:** 2012  
**Abstract:** It is difficult to understand the thinking of someone who attempts or dies by suicide. Some people seem to act impulsively while others seem engaged in premeditated and deliberate suicidal behavior. Both types of thinking can be deadly. Dr. Szanto will investigate decision profiles associated with a predilection to deliberate (planned attempts with high medical lethality) versus impulsive (less premeditated attempts often causing less medical damage) suicide attempt. Decision-making abilities will be assessed at four complementary levels: 1) behavioral (decision-making in the laboratory); 2) cognitive (decision making problems); 3) self-report (of problem-solving, impulsivity, and interpersonal reactivity); and 4) real-life (history of poor decisions). The study will enroll and assess 90 individuals ages 40 to 60, including deliberate and impulsive suicide attempters, depressed individuals without suicide attempts, and non-psychiatric controls. Dr. Szanto hypothesizes that she will find an association between the type of attempt that was made and the pattern of performance and responses obtained on the decision-making measures. These varying patterns may help us to understand different pathways to suicide attempts.

**Funding Organization:** American Foundation for Suicide Prevention  
**Study Title:** White Matter Integrity and Suicide Attempt History  
**Principal Investigator:** Doreen Olvet  
**Year When Study First Received Funding:** 2012  
**Abstract:** The fibers in the brain’s white matter serve as information networks for sending messages throughout the brain. Their structure and functioning may relate to impulsiveness, as well as to suicide intent and lethality in people who have made a suicide attempt. Dr. Olvet will use an imaging technique called Diffusion Tensor Imaging (DTI) to discover how the structural integrity of white matter cells in the brain differs among three groups of participants: depressed individuals who have made a suicide attempt, depressed individuals who have not attempted suicide, and individuals with no psychiatric history. Dr. Olvet expects to find that individuals with a history of suicide attempts will have less white matter integrity than those who have not attempted suicide. She will also attempt to identify specific paths, or tracts, that might play a role in suicidal behavior.
Funding Organization: American Foundation for Suicide Prevention
Study Title: Life Stress and Affect Regulation in Multiple and First Time Adolescent Suicide Attempters
Principal Investigator: Richard Liu
Year When Study First Received Funding: 2012
Abstract: Given that a previous suicide attempt is the best predictor of future suicidal attempts, Dr. Liu will interview adolescents who are hospitalized for a suicide attempt and compare those with previous suicide attempts to those who have made only one attempt. He hypothesizes that, prior to their most recent attempt, adolescents with multiple attempts will 1) have experienced lower levels of precipitating life stress outside of their control (e.g., death of a family member); 2) have experienced higher levels of life stress that are in part influenced by their behavior (e.g., fight with parents); 3) have greater difficulty managing their emotions; and 4) have a greater likelihood of having a combination of both life stress and difficulties in managing emotion.

Funding Organization: American Foundation for Suicide Prevention
Study Title: Person-specific Modeling of Suicidal Ideation in Sexual Minority Youth
Principal Investigator: Katerina Sinclair
Year When Study First Received Funding: 2012
Abstract: While many factors have been identified that are associated with suicidal ideation and behavior, it is difficult to predict what factors are functioning to produce such behavior in a particular individual. The goal of Dr. Sinclair’s study is to develop a method to predict changes in the severity of suicidal ideation and depression in an individual over time. She is particularly focused on sexual-minority youth and the application of Joiner’s model of suicide. Her primary aim is to demonstrate that following individuals intensively over time will allow for the identification of factors that increase and decrease suicidal ideation and behavior. Using this novel approach, she hypothesizes that: (1) individual models will predict changes in suicidal ideation more effectively than population models; (2) factors that affect suicidal ideation will be specific to each youth and their impact will change over time; and (3) individual models will successfully identify protective factors and interventions that reduce suicidal ideation over time in each youth. In order to test this, three to five youth who report high levels of suicidal ideation will be recruited from a larger, multisite, longitudinal study of suicidal ideation in LGBT youth. Each participant will complete a 120-day daily assessment using a battery of instruments that assess suicidal ideation and depression, stressful experiences, coping skills, and treatment received. She will examine and compare the patterns identified for each youth to understand suicidal ideation and behavior.

Funding Organization: American Foundation for Suicide Prevention
Study Title: Posttraumatic Stress Disorder and Suicide among Massachusetts Veterans
Principal Investigator: Jaimie Gradus
Year When Study First Received Funding: 2012
Abstract: The rate of suicide among military veterans has been found to be higher than in the general population. Post-traumatic stress disorder (PTSD) has been associated with suicide and nonfatal suicidal acts by some researchers but not others, depending on their methodology. Dr. Gradus will use data from the VA hospital system in Massachusetts from 2000 to 2007, including data available from approximately 18,000
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veterans with PTSD and 90,000 without PTSD, to examine the association between suicide and nonfatal suicidal acts in veterans with PTSD. She hypothesizes that: (1) the rate of suicidal behavior (suicide attempts and suicides) among veterans diagnosed with PTSD will be higher than the rate of suicidal behavior among VA patients without PTSD, and (2) the rate of suicidal behavior among veterans with PTSD and depression will be greater than for those with either a PTSD or depression diagnosis alone. She will examine the role of demographic characteristics, psychiatric diagnosis, and treatment to help clarify the relationship between PTSD and suicidal behavior in veterans who are treated in the VA hospital in Massachusetts.

Funding Organization: Brain & Behavior Research Foundation
Study Title: Neurobiological Predictors of Suicide in Bipolar Disorder
Principal Investigator: Alison Gilbert
Year When Study First Received Funding: 2011
Abstract: Alison Gilbert, Ph.D., of Zucker Hillside Hospital, Feinstein Institute for Medical Research, North Shore-Long Island Jewish Health System, wants to uncover the underlying biology linking impulsivity, cognition and suicidal behavior in people with bipolar disorder. She proposes to use a neuroimaging method called diffusion tensor imaging to take pictures of the white matter, tracts that connect various brain regions to one another, and compare the images from a group of bipolar patients who have made an unambiguous suicide attempt with a group of bipolar patients who have never attempted suicide. She hypothesizes that there will be reduced integrity in the white matter in the orbitofrontal cortex of the brain in those who have attempted suicide versus those who have not. The goal of the trial is to find reliable biological markers to predict which patients may pose the greatest suicide risk.

Funding Organization: Brain & Behavior Research Foundation
Study Title: Remediating Decision-Making Deficits in Depressed Subjects at High Risk for Suici
Principal Investigator: Marcelo Berlim
Year When Study First Received Funding: 2013
Abstract: Marcelo T. Berlim, M.D., M.Sc., of McGill University, will use repetitive transcranial magnetic stimulation (rTMS), a safe, noninvasive method of stimulating brain activity, in an effort to relieve symptoms in depressed patients at high risk for suicide. Sixty patients, age 18 to 60, with a current major depressive episode of at least moderate intensity and a lifetime history of at least one serious suicide attempt, will be enrolled in the study. The hope is that the trial will provide a better understanding of the neurobiological basis of a well-known predisposing factor for suicidal behavior, namely decision-making deficits, and that high-frequency rTMS can improve those deficits, thus reducing suicide risk.

Funding Organization: Brain & Behavior Research Foundation
Study Title: Genetic Contribution to Suicidal Behaviors
Principal Investigator: Molly Adrian
Year When Study First Received Funding: 2013
Abstract: Both hypothalamic-pituitary-adrenal (HPA) axis dysregulation and childhood adversity shape individual responses to stress and are associated with increased risk for suicidal behaviors. The aim of this proposal is to examine how 4 single nucleotide polymorphisms (SNPs) affect suicidal behaviors. First, utilizing
Bayesian statistical models, we will explore if in the context of chronic family adversity 4 SNPs directing HPA axis activity have an appreciable influence on suicidal behaviors during adolescence. Next, we will examine if intermediate individual characteristics (i.e., endophenotypes) of emotion regulation, hopelessness, and impulsive-aggression, mediate the effects of genetic contributions to the HPA axis onto suicidal behaviors. We hypothesize that SNPs associated with the HPA dysregulation will influence hopelessness, which will subsequently impact suicidal ideation. Additionally, we hypothesize that SNPs will impact emotion regulation and impulsive-aggression traits, which will then directly affect suicide attempts.

**Funding Organization:** Brain & Behavior Research Foundation  
**Study Title:** The Development of a Longitudinal Endophenotype for Aggressive and Impulsive Suicidal Behavior  
**Principal Investigator:** Rashelle Jean Musci  
**Year When Study First Received Funding:** 2013  
**Abstract:** With recent release of the 2012 National Strategy for Suicide Prevention (NSSP), suicidality has come to the forefront as a major public health concern. With suicide being the 10th leading cause of death, it is essential for developers of prevention and intervention programs to know and understand the etiology of suicidal behavior, and more specifically, understand how biology may play a role in the development of such behaviors. Previous work has attempted to identify direct links between genetic variation and suicide behavior. These analyses have resulted in a number of conflicting results. Due to this, researchers have begun to explore the use of endophenotypes to replace the traditional outcome in genetic analyses. An endophenotype is a term developed in the genetic epidemiology to compile behavioral phenotypes that have a clear genetic origin. An endophenotype associated with suicidal behavior is one characterized by high levels of aggression and impulsivity, the genetic origins of which have not yet been explored in an African American population. The current study aims to first estimate the longitudinal endophenotype of aggression and impulsivity as it relates to suicidality. Further, this study explores the relationship between the established longitudinal endophenotype and selected gene systems. These gene systems will be chosen based on previous literature as well as results from existing, publicly available datasets. We hypothesize that genes within the serotonergic system will be significantly related to the aggressive/impulsive suicide phenotype because of previous findings linking suicide attempts, aggression and impulsivity. These aims will be accomplished using an existing dataset from the Center for Prevention Research. This longitudinal preventive intervention began in 1993 with 799 primarily African American first-graders from the Baltimore City Public Schools. Data collection has continued yearly, with blood or saliva samples collected during the 19-21 year follow-up. Measures of aggressive and impulsive behavior were collected from parents, teachers and peers of the participants. Suicidal behavior was collected from participants annually with a self-report measure. DNA was collected via blood or saliva and genotyped using a genome wide Affymetrix 6.0 microarray. All genotypic data required passing quality control in order to be used in any analyses.
Funding Organization: Department of Defense
Study Title: A Taxometric Investigation of Suicide
Principal Investigator: Jill Holm-Denoma & Tracy Witte
Year When Study First Received Funding: 2013
Abstract: Problem: It is not currently known if suicide risk is a categorical or dimensional phenomenon. This may explain why current suicide risk assessment procedures have limited predictive validity. Hypothesis: Military personnel at “high risk” for suicide are qualitatively distinct from those at “low risk” for suicide. Military Relevance: As suicide rates among military personnel continue to rise, effectively determining how to classify suicide risk is critical. Valid classification impacts: 1) Assessment of suicide risk; 2) Allocation of suicide prevention programs; 3) Allocation of research resources.

Funding Organization: Department of Defense
Study Title: A Novel Approach to Identifying Behavioral & Neural Markers of Active Suicide Ideation
Principal Investigator: Beeta Homaifar & Melissa Amick
Year When Study First Received Funding: 2013
Abstract: Study will assess the cognitive and neural vulnerabilities through which actively suicidal OEF/OIF/OND Veterans become overtaxed during a novel experimental task that induces emotional and cognitive stress. The authors hypothesize that during a working memory task with induced cognitive and
emotional stress, we will demonstrate the 1) cognitive, 2) functional, and 3) structural changes in the frontal lobes and amygdala that are markers unique to SI. Identifying markers of clinically significant SI will improve military suicide prevention programs by focusing interventions to address cognitive and neural vulnerabilities. These markers can serve as objective outcome measures to determine intervention efficacy.

**Funding Organization:** National Institutes of Health  
**Study Title:** Self-Harm and Drug Use in Adolescents  
**Principal Investigator:** Donald Dougherty  
**Year When Study First Received Funding:** 2008  
**Abstract:** This subproject is one of many research subprojects utilizing the resources provided by a Center grant funded by NIH/NCRR. The subproject and investigator (PI) may have received primary funding from another NIH source, and thus could be represented in other CRISP entries. The institution listed is for the Center, which is not necessarily the institution for the investigator. While cross-sectional studies show that drug abuse, impulsivity, serotonin dysregulation, and stressful life events are associated with suicide, studies examining the specific relationships of these factors are limited. A NIDA-sponsored workgroup was formed to identify gaps in the literature and priorities for future research. Studies have typically related individual measures of impulsivity or serotonin (5-HT) markers to self-reports of previous suicidal behaviors and drug abuse cross-sectionally, but they have not determined the predictive validity of these measures in determining future drug abuse and suicidal behaviors. Furthermore, the relationships between impulsive behavior and 5-HT, while often included in theoretical models of suicide, have not been firmly established. Also, how the combination of factors defined within these models affects the developmental trajectories of drug abuse and suicidal behaviors is unknown. The purpose of this longitudinal study is to examine the interrelationships among impulsivity, 5-HT, stressful life events, and the dual outcomes of drug use and different types of suicidality in high-risk adolescents. Our goal is to determine the direct and interactive contributions of these factors to the developmental trajectories of suicidal behavior and drug abuse.

**Funding Organization:** National Institutes of Health  
**Study Title:** Emotional and Behavioral Dysregulation in Borderline Personality Disorder  
**Principal Investigator:** Edward Selby  
**Year When Study First Received Funding:** 2008  
**Abstract:** DESCRIPTION (provided by applicant): Borderline personality disorder (BPD) is a severe disorder in which individuals often engage in extreme behaviors such as self-injury, impulsive behaviors, substance abuse and suicidal behavior. Individuals with BPD symptoms utilize the health care system (e.g., visits to physicians, emergency rooms, and hospitalizations) at alarmingly high rates (Hueston, Mainous, & Schilling, 1996) and are at extremely high risk for death by suicide. This makes BPD a significant public health concern. Although successful treatments have been developed for BPD (Dialectical Behavior Therapy; Linehan, 1993), little attention has been given to understanding the underlying causes and functional aspects of the maladaptive behaviors seen in BPD, valuable information for the treatment of this disorder. Linehan’s (1993) theoretical model of BPD asserts that individuals with BPD have significant problems with emotion dysregulation in that they 1) have a heightened sensitivity to emotional stimuli, 2) experience emotions as extremely intense, and 3) they have a slow return to emotional baseline. Research also suggests that the maladaptive behaviors of individuals with BPD may serve the common purpose of emotion regulation. Recent findings in the field of
emotion science provide evidence that rumination (a form of cognitive emotion dysregulation) may account for the emotion dysregulation seen in BPD. Rumination is defined as focusing attention and thoughts on the causes and consequences of emotionally relevant stimuli. Consequently, rumination has been shown to magnify and perpetuate negative affect; intense negative affect, in turn, may result in increased attention to emotionally relevant stimuli - potentially resulting in a cycle that causes a "cascade" of intense emotions (Selby et al., in press). The proposed studies will examine the role of cognitive emotion dysregulation (defined as high levels of rumination) in BPD, as well as examine the role that maladaptive behaviors (including suicidal behaviors) have in interfering with rumination. Study 1 will examine the role of rumination in BPD with an induced rumination on negative affect procedure. A subsequent pain tolerance test with a cold-pressor will provide a proxy for self-injury, and information about the distracting quality of pain. The second study will examine the contextual and ruminative features surrounding behavioral dysregulation in BPD with an Ecological Momentary Assessment protocol. PUBLIC HEALTH RELEVANCE: This study will examine if real-time rumination and interpersonal problems tend to precede behavioral dysregulation in the daily life of BPD individuals, through the use of palm pilots. This study will also specifically examine if an interaction between rumination and interpersonal problems is associated with NSSI in individuals with BPD.

Funding Organization: National Institutes of Health
Study Title: CORE—Principal Research
Principal Investigator: Lynn Martire
Year When Study First Received Funding: 2009
Abstract: Principal Research seeks to increase the number and availability of evidence-based interventions applicable to elderly persons at high risk for depression and its complications, to those with difficult to treat mood disorders seen within the specialty mental health sector, and to those seen in the primary care sector, in rehabilitation centers, and in nursing home and other long term care settings. Intervention studies will address the following themes: (1) preventing depression and suicide in elderly persons at high risk; and improving, preventing, or delaying cognitive and functional impairments in elderly with depression; (2) improving treatment for difficult to treat mood disorders in later life (e.g., bipolar disorders, psychotic depression, and unipolar major depression responding only partially to first line treatment); and (3) identifying and removing barriers to effective depression treatment in community clinical settings. Cutting across these themes is the Center objective (4) of using infrastructure support to enhance research-training opportunities in mental health and aging and in community-based participatory research. These themes capture our movement from efficacy to effectiveness research, to services, dissemination, and practice research, as mandated in the NIMH Council report, Bridging Science and Service. To this end the bidirectional linkages between the Principal Research Core and the Research Network Development Core are of critical scientific importance.

Funding Organization: National Institutes of Health
Study Title: 1/2-Familial Pathways to Early-Onset Suicide Attempt
Principal Investigator: David Brent
Year When Study First Received Funding: 2009
Abstract: DESCRIPTION (provided by applicant): This 5-year, two-site A2 competitive renewal of "Familial Pathways to Early-Onset Suicide Attempts" seeks to identify familial and individual precursors of early-onset
suicidal behavior and mechanisms by which suicidal risk is transmitted from parent to child. The cohort consists of 308 offspring of 135 probands with major depressive disorder (MDD) and a history of suicide attempt and a comparison group of 232 offspring of 120 non-attempters probands with MDD, all of whom have been followed for an average of 3.8 years. The aims of the study are to: (1) continue annual follow-up of offspring of attempters and non-attempters in order to document incident and recurrent suicide attempts; (2) characterize all subjects, probands and offspring, on four putative intermediate phenotypes (IP) (impulsive aggressive traits, early-onset depression, neuropsychological function, cortisol response to stress) as well as other risk (e.g., child abuse and neglect) and protective factors (e.g., family cohesion) for suicidal behavior; and (3) examine the role of IPs in mediating the familial transmission of suicidal behavior and predicting new-onset suicide attempts both alone and in interaction with early childhood abuse and neglect. In a projected 4,693 person years of follow-up, a total of 67 new-onset suicide attempts are expected, which will allow for adequate statistical power to test our hypotheses that IPs are familially transmitted, and mediate the familial transmission of suicidal behavior. The identification of IPs will facilitate future genetic studies of suicidal behavior. This study sample is unique because it permits identification of risk factors for familial transmission of suicidal behavior, and the identification of precursors of early-onset suicidal behavior. Because there are now no empirically validated interventions for suicidal youth, the findings from this unique cohort should help to frame treatment targets in high-risk families and individuals designed to alter prodromal at-risk behavior and psychopathology and prevent future suicidal behavior. This study is of public health importance because suicidal behavior is the single biggest risk factor for completed suicide, which is the third leading cause of death among adolescents and young adults in the United States. The aims of this study are consistent with several priorities of the NIMH and the Division of Pediatric Translational Research (DPTR): (1) reduction of the public health burden of suicide and suicidal behavior; (2) inclusion of family-genetic approaches to elucidate the interplay of biological and environmental factors to childhood psychopathology and to identify behavioral and biological markers of vulnerability and resilience; and (3) research that is likely to lead to novel psychosocial and pharmacological preventive and therapeutic interventions. This application is from the Pittsburgh site (Principal Investigator: David Brent, MH56612). PUBLIC HEALTH RELEVANCE: This study, "Familial Pathways to Early-Onset Suicide Attempts," seeks to identify the familial and individual precursors of early-onset suicidal behavior and the mechanisms by which suicidal risk is transmitted from parent to child. We anticipate that certain traits, namely impulsive aggressive traits, early-onset depression, memory and decision making ability, and a greater physiological reaction to stress (measured by cortisol secretion) are familial and will: (1) explain how suicidal behavior runs in families; (2) predict suicidal behavior in the children of parents who have attempted suicide; and (3) yield intermediate phenotypes that can advance genetic studies of suicidal behavior. This study is important because suicide and suicidal behavior are leading causes of mortality and morbidity among adolescents, there are currently no empirically validated interventions to prevent or treat adolescent suicidal behavior, and the results of this study could frame targets for prevention and treatment.
suicidal behavior and mechanisms by which suicidal risk is transmitted from parent to child. The cohort consists of 308 offspring of 135 probands with major depressive disorder (MDD) and a history of suicide attempt and a comparison group of 232 offspring of 120 non-attempters probands with MDD, all of whom have been followed for an average of 3.8 years. The aims of the study are to: (1) continue annual follow-up of offspring of attempters and non-attempters in order to document incident and recurrent suicide attempts; (2) characterize all subjects, probands and offspring, on four putative intermediate phenotypes (IP) (impulsive aggressive traits, early-onset depression, neuropsychological function, cortisol response to stress) as well as other risk (e.g., child abuse and neglect) and protective factors (e.g., family cohesion) for suicidal behavior; and (3) examine the role of IPs in mediating the familial transmission of suicidal behavior and predicting new-onset suicide attempts both alone and in interaction with early childhood abuse and neglect. In a projected 4,693 person years of follow-up, a total of 67 new-onset suicide attempts are expected, which will allow for adequate statistical power to test our hypotheses that IPs are familially transmitted, and mediate the familial transmission of suicidal behavior. The identification of IPs will facilitate future genetic studies of suicidal behavior. This study sample is unique because it permits identification of risk factors for familial transmission of suicidal behavior, and the identification of precursors of early-onset suicidal behavior. Because there are now no empirically validated interventions for suicidal youth, the findings from this unique cohort should help to frame treatment targets in high-risk families and individuals designed to alter prodromal at-risk behavior and psychopathology and prevent future suicidal behavior. This study is of public health importance because suicidal behavior is the single biggest risk factor for completed suicide, which is the third leading cause of death among adolescents and young adults in the United States. The aims of this study are consistent with several priorities of the NIMH and the Division of Pediatric Translational Research (DPTR): (1) reduction of the public health burden of suicide and suicidal behavior; (2) inclusion of family-genetic approaches to elucidate the interplay of biological and environmental factors to childhood psychopathology and to identify behavioral and biological markers of vulnerability and resilience; and (3) research that is likely to lead to novel psychosocial and pharmacological preventive and therapeutic interventions. This application is from the New York site (PI: J. John Mann, MH056390). PUBLIC HEALTH RELEVANCE: This study, "Familial Pathways to Early-Onset Suicidal Behavior," seeks to identify the familial and individual precursors of early-onset suicidal behavior and the mechanisms by which suicidal risk is transmitted from parent to child. We anticipate that certain traits, namely impulsive aggressive traits, early-onset depression, memory and decision making ability, and a greater physiological reaction to stress (measured by cortisol secretion) are familial and will: (1) explain how suicidal behavior runs in families; (2) predict suicidal behavior in the children of parents who have attempted suicide; and (3) yield intermediate phenotypes that can advance genetic studies of suicidal behavior. This study is important because suicide and suicidal behavior are leading causes of mortality and morbidity among adolescents, there are currently no empirically validated interventions to prevent or treat adolescent suicidal behavior, and the results of this study could frame targets for prevention and treatment.

**Funding Organization:** National Institutes of Health  
**Study Title:** Functional Magnetic Resonance Imaging Markers of Early-Onset Suicide Attempt  
**Principal Investigator:** Lisa Pan  
**Year When Study First Received Funding:** 2009  
**Abstract:** DESCRIPTION (provided by applicant): The proposed application will provide the candidate with the needed expertise to establish an independent research career focusing on the investigation of the neurobiology suicide attempt in children and adolescents. The applicant is a child and adolescent psychiatrist
who proposes to obtain multidisciplinary training from mentors in suicidology and functional neuroimaging, with a panel of experts in childhood neurobiology, child development, neuroimaging, and data analysis. We propose to use established methods in functional neuroimaging and neuroscience to characterize the neurobiology underlying early onset suicide attempt. We will assess these adolescents, and age-matched psychiatric controls and healthy controls with well-established neurocognitive tasks. We hypothesize that history of suicide attempt in adolescents will be associated with differences in patterns of neural activity compared with both psychiatric and healthy controls. The primary objective of this research project is to examine the neural circuitry underlying traitdependent abnormalities in cognitive and emotion processing in adolescents with depression with and without history of suicide attempt, by focusing on the following areas: emotional processing, cognitive control, and risky decision-making, that have been demonstrated to recruit ventral and dorsomedial prefrontal cortices and amygdala and ventral striatum, dorsal prefrontal cortical regions, and ventromedial and dorsomedial prefrontal cortices, respectively. Our study of the neural circuitry of adolescent suicide attempt is important in that it will help to more precisely define: 1) cognitive and affective processing abnormalities associated with suicidal behavior; 2) functional neurocircuitry related to these neurocognitive abnormalities; and, in turn, 3) the relationship between these abnormalities and onset and history of suicidal behavior. Increased understanding of these neural markers will have a significant impact upon the future targeting of treatment and prevention efforts to improve the long-term outcome of individuals with suicidal behavior. This is the first study of its kind in a pediatric population. The functional neuroimaging instruction, didactics, coursework, and clinical research training, sponsored by Mary Phillips, M.D., M.D. (Cantab), Director of the Functional Neuroimaging Program, and David Brent, M.D., Endowed Chair in Suicide Studies, will prepare the candidate to perform multidisciplinary cognitive neuroscience research in adolescent suicide prevention. PUBLIC HEALTH RELEVANCE: Identification of markers for suicide risk and increased understanding of the cognitive neuroscience of suicide attempt may have a significant impact upon the future design and monitoring of treatment and prevention efforts to prevent death and improve the long-term outcome of individuals with suicidal behavior. This is the first study of its kind in adolescents.

**Funding Organization:** National Institutes of Health  
**Study Title:** Cognitive and Affective Neuroscience of Decision-Making in Late-Life Suicide  
**Principal Investigator:** Alexandre Dombrovski  
**Year When Study First Received Funding:** 2009  
**Abstract:** DESCRIPTION (provided by applicant): Brain mechanisms of vulnerability to suicide in old age remain unclear, and very few researchers study the neurobiology of late-life suicide. In particular, the field of suicide research lacks an understanding of how psychological and cognitive markers of suicidal risk (hopelessness, executive dyscontrol) relate to brain markers identified in post-mortem and imaging studies. The applicant - a geriatric psychiatrist with a clinical background in late-life suicide and in the treatment of late-life depression - views suicide as an outcome of an altered decision process, a view supported by preliminary behavioral and imaging data. Thus, the applicant's career goals are to apply advances in the basic neuroscience of decision-making to investigate the brain mechanisms of late-life suicide and, in the future, to identify intervention targets. This approach aims to bridge existing cognitive research on suicidal diathesis with basic and clinical neuroscience. This will be achieved through training in functional magnetic resonance imaging (fMRI; including computational model-based fMRI), in neurobiology of decision-making, and in using neuroscience models to identify intervention targets. An fMRI study of decision-making in elderly depressed suicide attempters focused on disruptions in the processing of value signals in the ventromedial and ventrolateral prefrontal
cortex will serve as a vehicle for proposed training. Proposed training and research will be supported by the Advanced Center for Interventions and Services Research for Late-Life Mood Disorders directed by CF. Reynolds (mentor), G.J. Siegle's fMRI lab (co-mentor), and L. Clark's imaging lab (Cambridge, UK). Taking advantage of the neuroimaging resources at the University of Pittsburgh, H.J. Aizenstein will help the applicant to overcome challenges in MR imaging of the aging brain and M.L. Phillips will aid in refining the neural model and developing a life-span perspective on decision-making in suicide. K. Szanto will help the applicant sharpen clinical characterization and manage suicidal risk. An ROI geared towards identifying intervention targets should result from this work. PUBLIC HEALTH RELEVANCE (See instructions): Worldwide and in the US, the elderly have the highest suicide rate of all age groups - a public burden likely to increase as US population ages and access to firearms is legally upheld. Current prevention approaches are not selective, targeting mainly depression. Insight into brain mechanisms will help identify elderly at risk for suicide and develop neuroscience-based interventions.

**Funding Organization:** National Institutes of Health  
**Study Title:** Neural Substrates of Emotion Dysregulation and Self Injury  
**Principal Investigator:** Christina Derbidge  
**Year When Study First Received Funding:** 2009  
**Abstract:** DESCRIPTION (provided by applicant): Self-inflicted injury (SII) in adolescents is a significant risk factor for later suicide and psychopathology in adulthood, and may be a developmental precursor of borderline personality disorder (BPD). Consistent with Linehan's biosocial theory of BPD, recent research among self-injuring adolescents suggests that they are emotionally dysregulated and that SII functions to regulate their intensely negative affect. Neuroanatomical models of emotion regulation circuitry, derived from extensive neuroimaging research, implicate ventral portions of the prefrontal cortex (PFC), the amygdala, the anterior cingulate cortex (ACC), and their interconnections. Though functional neuroimaging research on emotion regulation has burgeoned in recent years, very little imaging research has been conducted in samples selected specifically for SII, and no functional imaging studies have been conducted with at risk adolescents. Nevertheless, studies conducted with adults with BPD suggest that some of the same brain regions implicated in emotion regulation are altered. In the proposed research, functional magnetic resonance imaging will be used to examine neural correlates of emotional processing in adolescent girls who engage in SII, relative to depressed and normally developing adolescent girls. The paradigm, which includes passive viewing of negative emotion faces, is well established and has been used successfully and commonly with adults with BPD and MDD. PUBLIC HEALTH RELEVANCE: This research may lead to improved understanding the neural bases and etiology of SII in adolescents and may ultimately lead to improvements in diagnostic specificity, intervention targets, and prediction of treatment response. This research is consistent with the strategy for suicide prevention presented by the U.S. Department of Health and Human Services (DHHS) in 2001.

**Funding Organization:** National Institutes of Health  
**Study Title:** Biomarkers of Suicide Risk in Adolescents and Youth Adults: Factors that Co  
**Principal Investigator:** Hilary Blumberg  
**Year When Study First Received Funding:** 2009  
**Abstract:** DESCRIPTION (provided by applicant): This application addresses the broad Challenge Area (03) Biomarker Discovery and Validation and specific Challenge topic, 03-MH-101: Biomarkers in Mental Disorders
U.S. National Suicide Prevention Research Efforts: 2008-2013 Portfolio Analyses  
Short-Term Research Objective 1.C.

and is entitled: Biomarkers of Suicide Risk in Adolescents and Young Adults: Factors that Contribute to High Risk in Bipolar Disorder. The proposed study addresses a critical gap in knowledge that could have a major impact on progress in suicide prevention: identification of neural circuitry biomarkers of adolescent and young adult suicidality and the biological and environmental factors that contribute to their development. Each year, over one million individuals lose their lives to suicide worldwide, including more than 32,000 Americans. For adolescents and young adults, suicide is the 3rd leading cause of mortality. Suicide is preventable. The critical issues in its prevention are its early identification and addressing its risk factors; however, biomarkers for adolescent and young adult suicidality have not been identified. The development of biomarkers of suicide in adolescents and young adults is especially critical, as it could contribute not only to prevention of suicide in this age group, but evidence suggests that antecedents to suicide through adulthood are present in childhood and adolescence during which biological and environmental factors alter the development of neural circuitry leading to lifelong increases in suicide vulnerability. The proposed study brings together a new multidisciplinary team of investigators to focus on the identification of neural circuitry biomarkers of adolescent and young adult suicidality. This includes investigators with expertise that spans basic molecular neuroscience, genetic, development, child and adult psychiatry, neuropsychology and neuroimaging study. Adolescents and young adults with bipolar disorder (BD) with a history of suicide attempts will be compared to adolescents and young adults with BD without a history of suicide attempts, as well as adolescents and young adults who do not have a psychiatric disorder. Suicidality in BD will be the focus of this project, initiating this new program of research in adolescent/youth adult suicide, as BD is associated with one of the highest rates of suicide from amongst psychiatric disorders and is associated with a high rate of suicide in adolescents and young adults. Thus, study of development of suicide in BD could lead to the development of biomarkers associated with high risk for suicide and aid the development of prevention strategies that could be targeted to this high-risk group. The adolescents and young adults participating in this study will complete comprehensive assessments of psychiatric diagnosis, illness course features and symptoms, cognitive testing, and multi-modality magnetic resonance imaging brain scanning including functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI). Preliminary findings of the research team implicate the brain circuitry of emotion and impulse regulation. This brain circuitry will be investigated intensively using state-of-the-art brain scanning image analysis methods. Study of specific genetic variations will be performed and comprehensive information regarding psychosocial and environmental factors, including history of early stress and substance abuse, will be collected in order to study genetic and environmental factors that might influence risk for suicide. This project will initiate this program of research focused on identifying the causes and biomarkers for adolescent and young adult suicide. Long-term goals for this program include the development of new methods for early detection of risk for suicide and effective prevention methods. Relevance: Each year, over one million individuals lose their lives to suicide worldwide, including more than 32,000 Americans, and suicide is the 3rd leading cause of death in adolescents and young adults. It is preventable; however, in order to detect who is at risk and to develop effective prevention methods, identification of the brain circuitry biomarkers of suicidality in youth and the factors that contribute to the development of this circuitry are needed. This study would be one of the first investigations to utilize a comprehensive and intensive approach to elucidate brain circuitry biomarkers for suicide among adolescents and young adults and to study their genetic and environmental causes in a disorder associated with one of the highest risks for suicide among youths, bipolar disorder. PUBLIC HEALTH RELEVANCE: Each year, over one million individuals lose their lives to suicide worldwide, including more than 32,000 Americans, and suicide is the 3rd leading cause of death in adolescents and young adults. It is preventable; however, in order to detect who is at risk and to develop effective prevention methods, identification of the brain circuitry biomarkers of
suicidality in youth and the factors that contribute to the development of this circuitry are needed. This study would be one of the first investigations to utilize a comprehensive and intensive approach to elucidate brain circuitry biomarkers for suicide among adolescents and young adults and to study their genetic and environmental causes in a disorder associated with one of the highest risks for suicide among youths, bipolar disorder.

**Funding Organization:** National Institutes of Health  
**Study Title:** Identifying Cognitive Markers of Late-Life Suicide  
**Principal Investigator:** Katalin Szanto  
**Year When Study First Received Funding:** 2010

**Abstract:** DESCRIPTION (provided by applicant): Although depression commonly precedes late-life suicidal behavior, clinicians still cannot confidently identify depressed elderly who are most likely to attempt or die by suicide. Thus, there is a great need for better predictive models regarding suicidal behavior in the elderly. This revised R01 (MH085651) application is to investigate specific cognitive vulnerabilities to late-life suicidal behavior. We focus on features that may cause accumulation of stressors, undermine deterrents, and facilitate the final decision to take one's life. Our preliminary data indicate that deficits in (1) specific aspects of cognitive control that involve reward/punishment processing, and in (2) social cognition distinguish depressed elderly suicide attempters from depressed non-suicidal elderly, while the two groups show similar global cognition, working memory, and forward planning. Building on this preliminary evidence, this new-investigator R01 will include key cognitive probes in a large-enough sample to test hypotheses that impairments in decision-making, affective processing, reversal learning, and social cognition are specifically associated with suicide attempts in depressed elders. We propose to assess 100 suicide attempters, 80 non-suicidal depressed individuals, and 60 non-psychiatric control subjects, aged 60 and older, using theory-driven computerized assessments as well as traditional tests of cognitive performance. Participants will undergo extensive clinical characterization of their suicidal behavior, psychopathology, psychosocial stressors, physical health, possible brain injury from suicide attempts, and medication exposure. The three groups will be similar in demographic characteristics and medical illness burden, and the two depressed groups will have similar severity of depression. To determine whether the identified impairments persist over time despite changes in mood state, we will repeat cognitive assessments four months after baseline (when substantial clinical improvement can reasonably be anticipated based on our pilot data). We will also prospectively explore the effect of cognitive status on suicide-related outcomes during this follow-up period. In collaboration with the biostatistical team of our late-life depression center and our external statistical consultant, we propose to use multivariate analyses of covariance to compare cognitive functions across groups, as well as discriminant function analysis to create a compact cognitive battery and to test its utility for correctly identifying suicide attempters beyond known risk factors. We will use mixed effects models to examine stability of cognitive impairments across mood states. Statistical analysis will account for factors that may affect cognition: severity of depression, medical illness burden, serum anticholinergicity, and other relevant factors identified by preliminary analyses. This project builds upon an ongoing K23, where the PI has shown the feasibility of recruiting, assessing, and longitudinally following suicidal elders with a high rate of suicidal behavior during follow-up. The research project will be conducted at the University of Pittsburgh, in collaboration with the Experimental Psychology Department, University of Cambridge. PUBLIC HEALTH RELEVANCE: Understanding cognitive deficits associated with late-life suicidal behavior and their relationship to other risk factors may help to advance translational neuroscience in geriatric mental health, identify elderly people at risk for suicide, and...
help to develop individualized treatment strategies in the service of preventing suicide in older people, who have the highest suicide rate in the US. The compact cognitive battery for assessing suicide risk derived from this research can be used in future prospective studies and in clinical settings.

**Funding Organization:** National Institutes of Health  
**Study Title:** Suicide Endophenotypes and Molecular Mechanisms of Lithium Action  
**Principal Investigator:** Todd Gould  
**Year When Study First Received Funding:** 2010

**Abstract:** DESCRIPTION (provided by applicant): Suicide has a devastating impact on victims, their extended families, and public health in the United States, as well as throughout the world. Few treatments have been shown to reduce risk. An exception, supported by extensive clinical evidence, is that lithium is effective in reducing the risk of both attempted and completed suicide. However, the mechanisms underlying lithium’s antisuicidal actions are not yet known, limiting the development of improved prevention approaches. We intend to use the mouse as a model organism to elucidate molecular pathways by which lithium interacts with biological and behavioral factors associated with suicide in humans. However, rather than attempting the infeasible task of modeling suicide in mice, we will focus on approaches that assess mouse behavior in tests relevant to well validated endophenotypes (deconstructed components of complex behavioral phenotypes) associated with suicide including aggression and impulsivity. These endophenotypes will be used in combination with human genetic, biochemical, and pharmacological findings in suicide research to provide construct-valid animal models. Toward this end, clinical studies have implicated polymorphisms in a number of genes, including neuronal nitric oxide synthase (NOS1), with measures of impulsivity, aggression, and suicide. Similarly, the results of extensive research have implicated deficits in serotonin (5-HT) neurotransmission in the etiology of suicidal behavior as well as increased impulsivity and aggression. Data from preclinical and human genetic studies indicate that lithium may exert some of its mood stabilizing effects through inhibition of the enzyme glycogen synthase kinase-3! (GSK-3!). Intriguingly, emerging basic science evidence links NOS1 function, 5-HT neurotransmission, and GSK-3! activity suggesting that they may be causally linked in the pathophysiological processes relevant to the etiology and treatment of psychiatric diseases such as suicide, where impulsivity and aggression play a role. Thus, our Specific Aims are to: 1) Identify the effects of lithium on behavior in mice with genetically- and pharmacologically-induced decreases in 5-HT levels; 2) Identify the effects of lithium on behavior in mice with genetically- and pharmacologically-mediated deficiencies in nitric oxide synthase 1 (NOS1) activity; 3) Evaluate the role of glycogen synthase kinase-3!, a direct target of lithium, in modifying behaviors mediated by decreased 5-HT and NOS1 function. These studies will capitalize on current knowledge of lithium pharmacology and use mouse genetic knockouts and pharmacological approaches to dissect the molecular and neurobiological mechanisms whereby lithium may modify impulsive and aggressive behavior as well identify points of interaction between lithium and biological markers known to be associated with suicide. Public Health Relevance: The data derived from these studies should promote the development of improved pharmacological interventions to modify aggressive and impulsive behaviors thereby decreasing the risk of suicide across all diagnostic categories. PUBLIC HEALTH RELEVANCE: A completed suicide has a devastating impact on families, society, and public health. Few treatments have been shown to result in reduced risk; however, lithium treatment is effective, for unknown reasons, in reducing the risk of both attempted and completed suicide. This application proposes experiments in the context of endophenotype strategies that will reveal molecular mechanisms whereby lithium acts to exert its therapeutics effects.
Funding Organization: National Institutes of Health
Study Title: SMALL GRANT 4: Serotonin, Impulsivity and Suicide Attempts
Principal Investigator: Courtney Bagge
Year When Study First Received Funding: 2011
Abstract: This subproject is one of many research subprojects utilizing the resources provided by a Center grant funded by NIH/NCRR. Primary support for the subproject and the subproject's principal investigator may have been provided by other sources, including other NIH sources. The Total Cost listed for the subproject likely represents the estimated amount of Center infrastructure utilized by the subproject, not direct funding provided by the NCRR grant to the subproject or subproject staff. Given the clinical and public health significance of suicide, there is considerable interest in identifying factors that are associated with the diathesis for suicide attempts. There are well-established links between impulsivity and suicide attempts, but the nature of these associations remain unclear. One reason for this may be due to the heterogeneous nature of the construct of impulsivity, and it is largely unknown which specific facets of impulsivity relate to suicide attempts. The propensity for impulsive behavior has also been consistently linked to biological mechanisms implicated in suicidal behavior. Examining genetic associations with facets of impulsivity may provide a clearer signal in the search for serotonergic genes associated with suicide attempts. The present proposal seeks to examine the inter-relations among serotonergic genes, facets of impulsivity, and suicide attempts. To achieve this research goal, we will employ a case-control design, recruiting 200 psychiatric inpatients (100 suicide attempters and 100 non-suicidal controls). The two-session assessment will comprise 1) a comprehensive assessment (Axis I and II diagnoses, history of suicide attempt and characteristics of attempt, and facets of impulsivity), and 2) a laboratory session where participants will complete five behavioral measures of impulsivity. At the end of the comprehensive assessment, a saliva sample will be collected in order to examine polymorphisms in serotonergic genes (Tryptophan Hydroxylase [TPH2], and 5HTT). This study will provide preliminary data on the magnitude of the relation between polymorphisms of serotonergic genes and facets of impulsivity on suicide attempt, as well as the effect of polymorphisms of serotonergic genes on facets of impulsivity. These preliminary data and effect sizes will be used to inform the development of a larger study. Of note, an important aspect of this research is that it will establish biological, self-reported, and laboratory-based measures of distinct impulsivity processes relating to suicide attempts, as well as a suicide attempt characteristics (violent attempts). Given the high cost of suicidality to individuals and to the health care system, gaining a fine-grained understanding of impulsivity-suicide attempt associations is a critical step in allowing us to refine our theoretical models, improve our assessment tools, and suggest better treatments for suicide attempts.

Funding Organization: National Institutes of Health
Study Title: Impulsive Aggression, Neurocognition, and Suicidal Behavior in Depressed Youth
Principal Investigator: Jeffrey Bridge
Year When Study First Received Funding: 2011
Abstract: DESCRIPTION (provided by applicant): Major Depressive Disorder (MDD) is the most potent psychiatric risk factor for suicidal behavior in adolescents, yet most depressed youth never attempt suicide, diminishing the positive predictive value of a diagnosis of MDD in gauging the risk of future suicidal acts. Efforts to prevent youth suicide would benefit greatly from a deeper understanding of precursors and pathways to suicidal behavior in depressed youth, particularly if such knowledge informs the development of
effective risk evaluation and intervention strategies. Knowledge of measurable factors that increase the risk of future suicide attempts in depressed adolescents could prove critical to efforts to prevent youth suicide by virtue of: 1) aiding in the recognition of depressed youth at especially heightened risk for suicide, who at a minimum may require closer supervision and containment; 2) identifying targets for clinical intervention beyond the mood disorder per se; and, 3) contributing to the development of assessment tools and risk markers relevant to better gauging individual suicide risk and informing clinical intervention research with youth at risk for suicide. The proposed R01 application from an early stage investigator (ESI) will address critical gaps in knowledge by examining the role of impulsive aggression and neurocognitive functioning in the etiopathogenesis of suicidal behavior in adolescents with MDD. The central hypothesis is that impulsive aggression and deficits in executive function and decision making will contribute substantially to a model of future suicide attempts and add positive predictive value to traditional assessment approaches. Our hypothesis is informed by promising pilot work in which measures of impulsive aggression and decision making deficits sharply distinguished depressed adolescent suicide attempters from non-attempters. The design includes cross-sectional comparisons as well as a prospective longitudinal study of 300 depressed youth with and without a prior history of suicide attempt, followed from early to middle adolescence, the developmental period of highest risk for suicidal behavior. These results will contribute to the mission of the NIMH by improving our capacity to identify the temporal and likely causal sequence of antecedents to future suicidal acts in youth with MDD, thus framing targets for practical clinical risk assessment, intervention, and the prevention of suicidal behavior. PUBLIC HEALTH RELEVANCE: The severe consequences of adolescent suicidal behavior make the accurate identification of youth at high risk an important clinical, research, and public health objective. This is the first large-scale prospective study of the developmental antecedents of adolescent suicidal behavior to comprehensively address multiple risk and protective factors in depressed youth. With the use of a multi-method, state-of-the-art, and pilot tested approach for assessing impulsive aggression and an informative computerized battery of subtests of executive function and decision making, the proposed research may help to clarify the specific behavioral and neurocognitive pathways contributing to the etiopathogenesis of suicidal behavior. Thus, this work has the potential to inform the development of practical suicide risk evaluation tools, empirically-based treatments, and preventive interventions to reduce adolescent suicide.

Funding Organization: National Institutes of Health  
Study Title: Suicidal Ideation and Alcohol Outcomes in Emerging Adult College Drinkers  
Principal Investigator: Vivian Gonzalez  
Year When Study First Received Funding: 2011  
Abstract: DESCRIPTION (provided by applicant): This study is intended to advance our understanding of how suicidal ideation is functionally related to alcohol use and problems among emerging adult college students. Emerging adult college students have high rates of suicidal ideation and attempts and of alcohol use and problems. Among college students, individuals with suicidal ideation are more likely to binge drink and alcohol problems in this population are associated with increased rates of suicidal ideation and attempts. While the association between suicidality (ideation, attempts, and deaths) and alcohol is well documented in clinical and non-clinical populations, relatively few studies have applied relevant theory and research findings in both the areas of alcohol and suicidality to aid in the understanding of why they are linked. This study takes a conceptually driven and innovative approach to understanding the interplay of suicidal ideation and alcohol by developing and testing a model based on theory and research in the areas of both suicidality and negative
affect related-alcohol outcomes. The primary aim of this study is to examine a conceptual model, using structural equation modeling, of the associations among depression, severity of suicidal ideation, problem solving skills, the use of avoidant coping, drinking to cope with negative affect, impulsivity in response to negative affect (i.e., negative urgency), and alcohol use and problems. Participants will be 400 college men and women between the ages of 18 and 25, who are current drinkers and who have experienced (at a minimum) passive suicidal ideation. Unlike typical alcohol research, which has relied on self-report measures of problem solving to explore models of alcohol use, this study will include the innovation of using a performance-based measure of participants’ problem solving skills. This study also will use a more recent and refined measure of impulsivity in examining the relationships among suicidal ideation, impulsivity, and alcohol outcomes. Specifically, the role of negative urgency will be examined, as it is a facet of impulsivity found to be particularly associated with alcohol problems, it has been theorized to underlie the relationship between negative affect and alcohol problems, and our preliminary work suggests that it is particularly associated with suicidal ideation and alcohol problems among emerging adult college drinkers. This exploratory cross-sectional study will provide meaningful preliminarily data for longitudinal studies of the relationships among suicidality, coping skills, drinking to cope, negative urgency, and alcohol outcomes. The results of this study have the potential to contribute crucial knowledge by uncovering clinically malleable targets for secondary prevention and treatment efforts aimed at reducing suicidality and alcohol problems among emerging adults. PUBLIC HEALTH RELEVANCE: The results of this study have the potential to contribute knowledge crucial to the development of effective prevention and treatment efforts aimed at reducing suicidality (ideation, attempts, and deaths) and alcohol problems among emerging adult (18- to 25-year-old) college students, a population with high rates of both problems.

**Funding Organization:** National Institutes of Health  
**Study Title:** The Neurobiology of Self Appraisals and Social Cognition in Depressed Adolescents  
**Principal Investigator:** Karina Mendoza Quevedo  
**Year When Study First Received Funding:** 2011  
**Abstract:** DESCRIPTION (provided by applicant): The goal of the proposed study is to study the neural basis of aspects of self and social cognition - negative self-appraisals and elevated attention to negative emotional social signals - that are highly relevant to understanding the development of adolescent depressive disorders. Persistently negative self-appraisal and elevated attention to negative emotional social signals, (e.g. negative facial expressions) are key processes that denote risk for depressive disorders across the lifespan. These processes are particularly relevant to understanding risk for depression in adolescence, because this is a period during which there is rapid transformation in self appraisals and interpersonal social functioning as part of the key developmental task of forming a positive and coherent self-representation. Suboptimal resolution of this developmental task is linked to onset and recurrence of depressive disorders and risks for suicide in adolescence. Therefore, understanding the neural basis of negative self-appraisals and attention to negative facial expressions in adolescent depression will provide valuable insights into specific neural mechanisms of depression during this vulnerable developmental period to guide intervention strategies. Furthermore, this research will also help identify objective, neurobiological markers of adolescent depressive disorders that can be used in the future to detect those adolescents who may be most at risk of future depression or who are on a trajectory to a recurrent course of the illness.
Funding Organization: National Institutes of Health
Study Title: Behavioral and Physiological Predictors of Suicidal Behavior in Adolescents
Principal Investigator: Catherine Glenn
Year When Study First Received Funding: 2012
Abstract: DESCRIPTION (provided by applicant): The proposed research and training plan aims to advance our understanding of risk markers for suicidal behavior in adolescents, and to equip the applicant with the skills necessary to carry out independent longitudinal research in the areas of developmental psychopathology and suicide. There is an urgent need to identify ways to reduce rates of suicide among adolescents, and an important first step is to establish risk markers - or predictors - of suicide in this age group. The goal of the proposed research is to identify multiple behavioral and biological (psychophysiological) risk markers for suicidal behavior in adolescents. Importantly, these goals are also consistent with the National Institute of Mental Health (NIMH) Strategic Plan, which highlights the need for identifying biological and behavioral markers associated with clinically relevant problems. This goal will be achieved through the following specific aims: Aim 1. To examine the relation between two behavioral tasks for suicide (i.e., death/suicide IAT and suicide Stroop test) and suicidal behavior in adolescents. Aim 2. To examine the relation between reduced fear responding during suicide-related stimuli (psychophysiological measure) and suicidal behavior in adolescents. Aim 3. To examine additive and interactive associations between behavioral and psychophysiological predictors of suicidal behavior in adolescents. This work has the potential to better identify those adolescents at greatest suicide risk, who are in critical need of intervention. In line with state of the art methods used to diagnose physical conditions, this line of research aims ultimately to identify a short battery of tests that can be used to objectively assess risk for suicide in adolescents. These measures are ideal because they are brief, easily administered and scored, and thus could feasibly be used in an emergency department or inpatient setting to inform decisions about adolescents' admission and discharge from hospital care. Therefore, this program of research has the potential to significantly advance clinical science and to modernize the way the field assesses risk for suicidal behavior. The training plan in this application extends the applicant's previous research and clinical experiences in the following areas: developmental psychopathology, suicide, and longitudinal research design and analysis. In order to achieve these goals, the applicant has carefully assembled a team of sponsors and consultants to guide and support this project. Dr. Matthew Nock (sponsor) has expertise in suicide research and adolescent psychopathology. Dr. Ronald Dahl (consultant) is an expert in adolescent brain and pubertal development, as well as in early interventions. Finally, Dr. Terry Blumenthal has expertise in the startle reflex methodology - the physiological measure chosen for this project. In sum, the F32 training will advance the applicant's knowledge and expertise in three new areas and provide the foundation for a career as an independent clinical scientist. PUBLIC HEALTH RELEVANCE: Suicide is the third leading cause of death among youth ages 10 to 24 years, and alarmingly, the rates of suicide among this age group appear to be increasing. Although there is a critical need to identify adolescents at greatest risk for suicide, predicting suicidal behavior has proven difficult, and current strategies are insufficient. The goal of the current proposal is to identify behavioral and biological risk markers for suicidal behavior in adolescents in order to better detect those adolescents at greatest suicide risk, who are in urgent need of intervention.
**Funding Organization:** National Institutes of Health  
**Study Title:** Multi-Method Assessment of Emotion Reactivity: Translational Research in Suicide  
**Principal Investigator:** Michael Armey  
**Year When Study First Received Funding:** 2012  
**Abstract:** DESCRIPTION (provided by applicant): Although advances have been made towards understanding and treating suicidal behavior, suicide rates in this country have not fallen appreciably over the last decade. One explanation for our limited ability to effectively treat suicidality may be our limited understanding of the phenomenology of suicidality as it occurs in the real world. The proposed study, US-TREAT (Understanding Suicide: Translational Research in Emotional Reactivity Assessment Technology), is the first to apply a combination of multimethod in-hospital assessments and ecological momentary assessment (EMA) procedures post-discharge from inpatient care to model a translational phenotype of emotional reactivity, a clinically- and theoretically-important influence on suicidality, and its prediction of future suicidal ideation and behavior. A sample of 300 individuals hospitalized for suicidal ideation and behavior and 50 non-suicidal psychiatric comparisons will participate in a laboratory paradigm to assess physiological response (i.e., heart rate variability, skin conductance, & startle) to standardized environmental stimuli, EMA of emotional reactivity (i.e., affect, affective valence, and rate of change in affect over time), and genetic biomarkers (e.g. serotonin system, neurotrophins). To better characterize and predict the phenomenology of suicidality, we will use analytical models of cyclical processes (i.e., dynamical systems) to permit non-linear modeling of discrete aspects of emotion (i.e., intensity, rate of affect change, cyclicity, and damping) a influenced by experienced (i.e. EMA assessed) life stressors. The US-TREAT approach will provide critical insight regarding the phenomenology of suicidality with clear treatment implications. PUBLIC HEALTH RELEVANCE: Suicidal ideation and behavior are a serious public health concern in the United States. Current treatments for suicidality show limited efficacy, possibly due to our limited understanding of the phenomenology of suicidality as it exists in the real world. The present study proposes a multimethod assessment of an emotion reactivity translational phenotype for suicide, using a combination of laboratory measures and ecological momentary assessment methods, to explore the relationship between biological, experiential, and dispositional risk factors and suicidal ideation and behavior.

**Funding Organization:** National Institutes of Health  
**Study Title:** Cognitive Phenotype Neural Circuitry in vivo in Mood Disorders and Suicidal Beha  
**Principal Investigator:** Kevin Ochsner  
**Year When Study First Received Funding:** 2013  
**Abstract:** Over the past decade an important approach to describing and treating psychiatric disorders has been the application of cognitive neuroscience techniques to understanding the neural mechanisms underlying clinical dysfunction. For example, relative to healthy volunteers, individuals with major depressive disorder (MDD) may show hypoactivation of brain systems implicated in cognitive control (e.g. dorsal and ventrolateral prefrontal cortex, dIPFC and vIPFC) and hyperactivation of systems implicated in triggering emotional responses (e.g. the amygdala). Of particular interest is the extent to which such patterns may be related not just to MDD, but to suicide risk associated with depressive episodes. Although to date little functional imaging data have addressed this question, PET and postmortem work from Conte Center labs has shown that ventrolateral PFC and anterior cingulate hypofunction, as well as lower serotonin transporter binding in the amygdala and ventral/orbital PFC, may contribute to the risk of suicide or nonfatal suicide.
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attempts. This proposal seeks to clarify these links, building on an emerging model of the cognitive control of emotion in healthy adults to examine the neural bases of a specific cognitive strategy for emotion regulation - known as reappraisal - in individuals with major depressive disorder who have attempted suicide (MDD-Atts), who have never attempted suicide (MDD-Non-Atts), healthy volunteers (HVs) and currently non-depressed adult offspring of MDD-Atts who may be at higher risk for suicide (HRs). In Aims 1-3, we will compare the neural correlates of reappraisal performance of MDD-Atts, MDD-NonAtts, and HVs to determine whether depressed individuals in general, and those who attempt suicide in particular (Aim 1) generate stronger negative emotions or have greater trouble down-regulating them, (Aim 2) generate weaker positive emotions or have greater trouble up-regulating them, or show patterns of regulation-related activity under Aims 1 and 2 that (Exploratory Aim 3) are related to abnormalities in 5-HT function (see P3), childhood adversity, stress responsiveness and/or aggression (see CEC). In Exploratory Aim 4 we ask whether HRs show response patterns under Aims 1-3 that resemble Atts, thereby suggesting a diathesis towards suicide.

Funding Organization: National Institutes of Health
Study Title: Adult Follow-up of Girls with ADHD: Predictors, Mediators, and Mechanisms
Principal Investigator: Stephen Hinshaw
Year When Study First Received Funding: 2013
Abstract: DESCRIPTION (provided by applicant): Attention-deficit/hyperactivity disorder (ADHD) is well known to be a highly impairing and strongly persistent condition in boys and men, but knowledge about its long-term consequences in girls and women is severely limited. The core objective is to redress the major dearth of longitudinal data on females with ADHD via a rigorous, prospective, 15-year follow-up investigation, into the age span of the mid-20s, of a well-characterized, ethnically- and socioeconomically-diverse sample of girls with carefully diagnosed ADHD (n = 140), plus an age- and ethnicity/race-matched sample of comparison girls (n = 88). To the investigator's knowledge, this sample comprises the largest in existence of girls with this disorder, ascertained prior to adolescence. During earlier iterations of the current grant, participants were recruited and investigated between the ages of 6 and 12 years (Wave 1) and followed systematically in early to mid-adolescence (Wave 2, ages 11-18 years; 92% retention) and most recently in a 10-year follow-up in late adolescence/early adulthood (Wave 3, ages 17-24 years; 95% retention). Key aims for projected Wave 4 assessments, during the age span of 22-29 years, are to characterize outcomes of these women across multiple domains of functioning, including ADHD symptoms and subtypes, externalizing and internalizing behavior patterns (including antisocial behavior, mood disturbance, eating pathology, self-injurious and suicidal behavior), substance use/abuse, academic and vocational performance, neuropsychological skills, peer and family relations, health-related parameters, and service utilization. The overall goal is to understand trajectories of development, impairment, and (in some cases) positive adjustment, with the strongest focus on outcomes of major clinical and conceptual importance to female development: (a) educational attainment and employment status; (b) relationships/interpersonal functioning; (c) self-harm (i.e., suicidal behavior and self-injury, which were present at strikingly high rates during the 10-year follow- up); (d) executive functioning; and (e) health-related behaviors. The project's established methods of ascertaining positive adjustment will be followed. A related aim is to characterize baseline predictors and moderators and adolescent mediators of adult functioning, via stringent and sophisticated statistical methods. The proposed Wave 4 assessments feature psychometrically rigorous, multi-method, and multi-informant measures, many of which are identical or parallel across all four waves, facilitating growth-curve and growth-mixture modeling. Because of (i) major gaps in knowledge surrounding adult adjustment of women with ADHD and (ii) the potential for unique
findings to emerge during the age span of the mid-20s, examination of female developmental trajectories into adulthood is a key priority. Such aims will be met in this innovative and rigorous investigation, with the potential to enhance both basic and clinical science.

**Funding Organization:** National Institutes of Health  
**Study Title:** Suicidal Behavior: Aggression Subtypes, Childhood Adversity and Stress Response  
**Principal Investigator:** Barbara Stanley  
**Year When Study First Received Funding:** 2013  
**Abstract:** Aggression, childhood adversity, and the response to stress are all critical factors contributing to risk for suicidal behavior. However, the relationships among these variables and their relative contribution to suicidal behavior are not well-understood, in part, due to limitations in measures. Conceptually, there may be multiple dimensions or subtypes of each that contribute to suicide risk in different ways. The goal of this project is to characterize the extent and nature of aggressive behavior exhibited by participants, relate it to detailed assessments of types of childhood adversity as well as to situational, psychobiological responses to stress, and ultimately relate all of these to suicidal behavior in suicide attempters and non-attempters with major depressive disorder, high-risk offspring of suicidal individuals, and healthy volunteers. Aggressiveness will be assessed via interview, self-report and a behavioral measure (Point Subtraction Aggression Paradigm) to characterize the reactive vs. proactive nature of the behavior. While Reactive Aggression - characterized by acute responses to situational provocation and emotional volatility - is thought to underlie a substantial portion of suicidal behavior, Proactive Aggression - more deliberate behaviors with less overt emotional reactivity - has been less systematically studied, but has also been related to suicidal behavior. Childhood adversity will be assessed via the Childhood Trauma Questionnaire, a measure that distinguishes among physical abuse, sexual abuse, and emotional abuse/neglect. Our preliminary data indicate that the effect of past abuse on suicidal behavior is mediated by aggression. Stress response will be assessed via behavioral and Cortisol responses to the Trier Social Stress Test. Our preliminary data indicate that heightened Cortisol response to this stressor is evident in those with high impulsive aggression, a group that does not encompass all suicide attempters. Thus, there is a subtype of attempter who appears more sensitive to these situational stressors, but another subtype - currently poorly characterized - that does not. Ultimately, this project will make a major contribution toward characterizing alternative pathways to suicidal behavior, with potentially different underlying neurobiological mechanisms. In conjunction with data from PET receptor studies of the serotonin transporter (Project 3) and functional magnetic resonance imaging studies of emotional regulation (Project 4), these studies will identify relationships among these biological and behavioral measures that can provide targets for intervention more closely tailored to individual needs.

**Funding Organization:** Veterans Affairs  
**Study Title:** Executive Dysfunction and Suicide in Psychiatric Outpatients and Inpatients  
**Principal Investigator:** Lisa Brenner  
**Year When Study First Received Funding:** 2012  
**Abstract:** Individuals with a history of Traumatic Brain Injury (TBI) are at increased risk for suicidal behavior. Researchers have also found suicidal behavior to be associated with executive dysfunction as measured by indices of poor decision making, laboratory-measured impulsivity, and aggression; however, such studies were not focused on individuals with histories of moderate to severe neurologic disease or damage. To date, a
clearly defined study has not been conducted to explore the relationship between executive dysfunction, as a multidimensional construct and suicidal behavior in the vulnerable population of those with a history of moderate to severe TBI. The purpose of this study is to explore a potential risk factor that could impact assessment and intervention practices for those with moderate to severe TBI. Specifically, this study will examine whether the effect of suicidality on different dimensions of executive functioning is different for those with a history of moderate to severe TBI compared to those without a history of TBI.

**Funding Organization:** Veterans Affairs  
**Study Title:** Neurobiology of Impulsivity and Aggression in Female Veterans  
**Principal Investigator:** Erin McGlade  
**Year When Study First Received Funding:** 2012  
**Abstract:** The current study will use neuroimaging, clinical assessments, and neurocognitive testing to examine neurobiological and clinical features, including impulsivity and aggression, of female Veterans with self-directed violence compared to female Veterans without self-directed violence. We hypothesize the following: (1) females with and without suicidal behavior will differ in their anterior cingulate volume; (2) females with suicide attempts will have higher impulsivity and aggression than females without suicidal behavior; (3) anterior cingulate volume will be correlated with impulsivity, suicidal behavior and aggression.

**Funding Organization:** Veterans Affairs  
**Study Title:** The Influence of PTSD on Perceptions of Injury  
**Principal Investigator:** Nazanin Bahraini  
**Year When Study First Received Funding:** 2012  
**Abstract:** Given high rates of mTBI and PTSD co-morbidity in Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) Veterans, it is important to understand how PTSD interacts with cognitive processes (e.g., beliefs, perceptions) that have been shown to impact recovery and functioning following mTBI. The purpose of this pilot study is to examine the effect of PTSD on perceptions and beliefs about physical injury in Veterans with a history of combat mTBI or non-TBI injury. This research may provide a greater understanding of how co-occurring affective responses to trauma can impact the way individuals perceive and respond to different bodily injuries.