Short-Term Research Objective 1.B.

Identify biomarkers (e.g., genetic, epigenetic, immune function, neuropsychiatric profiles) and their interactions that are associated with current and future risk status.

Funding Organization: American Foundation for Suicide Prevention
Study Title: Urocortin 3 in Dorsolateral Prefrontal Cortex of Depressed Suicides
Principal Investigator: Garth Bissette
Year When Study First Received Funding: 2008
Abstract: We will determine whether urocortin 3 protein, the major endogenous brain ligand for the type 2 corticotropin releasing factor receptor, is increased in concentrations in the dorsolateral prefrontal cortex of subjects dying of suicide with depressive symptoms at the time of death. We will micropunch frozen sections of post mortem brain dorsolateral prefrontal cortex and measure the amount of urocortin 3 protein by sensitive and specific radioimmunoassay. Subjects dying of suicide with and without antidepressant drugs that were assessed for depressive symptoms at the time of death by psychiatric autopsy will be compared to age- and sex-matched controls dying of sudden death. We expect that we will find urocortin 3 protein levels to be increased in the depressed subjects relative to the non-depressed controls and this will indicate that stress circuits in a major executive control center of the brain are active during depression that leads to suicide. If urocortin 3 is elevated in the dorsolateral prefrontal cortex of subjects with depressive symptoms at the time of suicide then a drug that blocks the type 2 CRF receptors may be useful in preventing part of the impulsivity or hopelessness that contribute to suicide attempts. Such a drug might also function as an antidepressant.

Funding Organization: American Foundation for Suicide Prevention
Study Title: Cortisol Reactivity in the Prediction of Suicide Attempts in Borderline Personality Disorder
Principal Investigator: Eric Fertuck
Year When Study First Received Funding: 2008
Abstract: The key aim of this study is to investigate if cortisol (a stress hormone) changes in reaction to social stress can predict whether or not individuals with this borderline personality disorder have made are suicide attempters. This study will involve the administration of a standardized procedure that creates a moderate amount of social stress to individuals at high risk for suicide and to healthy comparison individuals. We will evaluate change in cortisol before, during, and after the stress, and compare our groups on cortisol changes. Finally, we will use this measure of stress reactivity to attempt to distinguish individuals who have made a suicide attempt from non-attempters, and to identify if cortisol reactivity differentiates the types of environmental “triggers” to suicide attempts. Identifying more specific and readily assessable environmental and biological indicators of stress reactivity, and how they may differentially predict vulnerability to suicide, should help prevention and treatment efforts for suicidal individuals such as many of those with borderline personality disorder. Our study of social stress cortisol reactivity and environmental “triggers” to predict suicide attempts in borderline personality disorder has the potential to contribute substantially to this effort.
Funding Organization: American Foundation for Suicide Prevention

**Study Title:** The Temporal Association between Substance Use and Suicidality among Adolescents with Bipolar Disorder

**Principal Investigator:** Benjamin Goldstein

**Year When Study First Received Funding:** 2008

**Abstract:** To characterize the nature and timing of substance use and suicidality in a high-risk sample of adolescents with bipolar disorders. This study will involve careful detailed assessment of substance use and suicidality in a sample of thirty adolescents (ages 12-18 years) with bipolar disorders. Adolescents diagnosed with bipolar disorders will be recruited from a specialty outpatient clinic if they have made a suicide attempt or had suicidal intentions/plans in the past year, and if they have become intoxicated with alcohol or used illicit drugs in the past year. Subjects will complete in-person assessment of overall psychiatric symptoms and status every three months, as well as telephone-administered measures of suicidality and substance use at monthly intervals through 9 months of follow-up. The anticipated findings of this pilot study will yield an estimate of the duration of the hazard period associated with acute substance use among high-risk adolescents with bipolar disorders and a history of suicidality. These findings will inform future applications for a large-scale study employing similar methodology, which will in turn inform research on risk assessment as well as targeted psychosocial and pharmacologic interventions.

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Funding Organization: American Foundation for Suicide Prevention

**Study Title:** A Prospective Study of Suicidal Ideation, Suicide Attempts, and Completed Suicide in Body Dismorphic Disorder

**Principal Investigator:** Katherine Phillips

**Year When Study First Received Funding:** 2008

**Abstract:** The primary aim of this study is to examine the following in 192 individuals with body dysmorphic disorder (BOD): 1) the rate and characteristics of suicidal ideation; 2) the rate and characteristics of suicide attempts; 3) the rate of completed suicide; 4) the relationship between severity of current suicidality, current BOD symptoms, and current depressive symptoms; and 5) predictors of suicidal ideation and suicide attempts. This study will involve 192 individuals who have participated in a prospective, longitudinal, observational follow-up interview study of the course and clinical features of body dysmorphic disorder who have already had annual interviews for up to 4 years of follow-up. These individuals will be recontacted and re-interviewed to obtain new information on suicidal ideation and suicide attempts. We will also determine the rate of completed suicide in this sample by searching the Social Security Death Index and other databases and by obtaining death certificates. Body dysmorphic disorder is a severe and relatively common illness that appears to be associated with high rates of suicidal ideation, suicide attempts, and completed suicide, although available data are very limited. By obtaining new and unique data on suicidality in BOD, this study: 1) will raise clinician awareness of the importance of identifying body dysmorphic disorder, monitoring these patients' suicidality, and focusing treatment on suicide prevention; and 2) by better characterizing suicidal ideation and attempts, this study will lay essential groundwork for the future development of a much-needed treatment for highly suicidal patients with body dysmorphic disorder.
U.S. National Suicide Prevention Research Efforts: 2008-2013 Portfolio Analyses
Short-Term Research Objective 1.B.

Funding Organization: American Foundation for Suicide Prevention
Study Title: Genetic Variation in Glutamate Receptor Subunits May Contribute to Suicidal Ideation Susceptibility in Pregnancy
Principal Investigator: Alicia Smith
Year When Study First Received Funding: 2009
Abstract: This study will examine if differences in genetic structure or expression of genes relevant for glutamate-mediated neurotransmission, previously implicated in suicidal ideation (SI), contribute to the risk of developing SI during the perinatal period, which is a common clinical problem. Glutamate-mediated neurotransmission is altered during pregnancy and, almost 30% of pregnant women with psychiatric illness experience SI. To examine if variations in glutamate-mediated neurotransmission contribute to the high rate of SI in women with psychiatric illness during the perinatal period, we will examine gene expression profiles of two glutamate receptor subunits during the pre-conception period, each trimester of pregnancy and postpartum to test if expression patterns of these genes are more common in those who develop SI. We will then determine if the frequency of genetic polymorphisms in these genes are more common in women who experience SI than those who do not and whether the polymorphisms can be associated with patterns of gene expression. This study will confirm previous findings and further characterize of role of genes needed for glutamate-mediated neurotransmission in SI. The potential contribution of these genes to SI is a valuable lead for understanding the causes of SI and developing a risk model for suicidal behavior.

Funding Organization: American Foundation for Suicide Prevention
Study Title: The Impact of RNA Editing on Suicide Risk
Principal Investigator: Monsheel Sodhi
Year When Study First Received Funding: 2009
Abstract: The key aim of this study is to investigate the diagnostic and molecular specificity of RNA editing in suicide, and to determine the influence of genetic variation on this process. The study will comprise statistically powerful investigations of postmortem brain tissue, from 369 subjects, including controls and subjects with schizophrenia, bipolar depression or major depression; of the subjects with psychiatric disorders, 38% are suicide cases. The aims of this investigation are to determine: 1) whether the influences of 5-HT2C RNA editing on suicide risk are specific to a diagnostic group; 2) if there is a generalized increase in RNA editing activity in dorsolateral prefrontal cortex due to altered activity of the ADAR enzymes or if the RNA editing changes observed in suicide are specific to the 5-HT2C transcript; and 3) genetic variation which may be influencing the RNA editing process in suicide. The current proposal aims to identify pathophysiological mechanisms by which suicidality could arise. Better understanding of this dysfunctional neurochemistry will facilitate the development of improved prediction and treatment of the underlying problem.

Funding Organization: American Foundation for Suicide Prevention
Study Title: Genome-wide Association Study of Attempted Suicide
Principal Investigator: Virginia Willour
Fiscal Year When Study First Received Funding: 2009
Abstract: Our goal is to compare the genomes of 1000 cases with a history of attempted suicide to the genomes of 2000 controls to identify genetic variation associated with an increased risk of suicidal behavior.
Short-Term Research Objective 1.B.

Genetic studies of suicidal behavior in families with bipolar disorder, major depression, and alcohol dependence all provide strong evidence that there are genetic risk factors for suicidal behavior. Our goal is to compare the genomes of 1000 cases with a history of attempted suicide to the genomes of 2000 controls to identify genetic variation associated with an increased risk of suicidal behavior. We will use this whole genome comparison to identify the top 3-5 suicidal behavior candidate genes to be studied in depth, with the goal of finding genetic variation that can eventually be used to identify subjects at increased risk for attempting suicide. Identifying genetic risk factors associated with suicidal behavior is an essential component of any suicide prevention program. It would allow for the identification of individuals at higher risk for suicidal behavior, would provide new therapeutic targets, and would facilitate the identification of the medications that increase or decrease suicidal behavior in individuals with this risk factor.

**Funding Organization:** American Foundation for Suicide Prevention

**Study Title:** Dissecting Serotonergic Influences on Impulsivity and Aggression

**Principal Investigator:** Luis Pennanen

**Year When Study First Received Funding:** 2009

**Abstract:** The key aim of the study is to use mouse molecular genetic approaches to elucidate the contributions of a specific neurotransmitter receptor, the serotonin 2C receptor, in regulating impulsive and aggressive behaviors. To determine whether complete loss of serotonin 2C receptor function leads to impulsive and/or aggressive behaviors, mice lacking functional serotonin 2C receptors will be assessed in specific behavioral tasks for impulsivity and aggression. Moreover, I will analyze the underlying neural mechanisms causing impulsive and/or aggressive behaviors in mice lacking functional serotonin 2C receptors. In a second aim, I will ask specifically which brain regions are important for impulsivity and aggression by genetically inactivating serotonin 2C receptors subpopulations in these target regions. Loss of behavioral inhibition leading to impulsive and aggressive behaviors is a key factor for suicidal behavior, and this is modulated by the serotonin system. Elucidation of the underlying mechanisms using a sensible model system for impulsivity/aggression could lead to new insights into the complex serotonergic modulation of both normal and pathological brain function, including suicide.

**Funding Organization:** American Foundation for Suicide Prevention

**Study Title:** Investigating Glial cell line-Derived Neurotrophic Factor (GDNF) in the Amygdala of Suicide Victims

**Principal Investigator:** Naguib Mechawar

**Year When Study First Received Funding:** 2009

**Abstract:** This postmortem study in suicide completers is aimed at studying cells using the growth and survival factor Glial cell line-Derived Neurotrophic Factor (GDNF) in the amygdala, a brain region previously involved in major depression. The distributions of GDNF, its main receptor (GFR1) and the GDNF-sensitive dopaminergic innervation will be analyzed in postmortem amygdalae from depressed suicide victims and age-matched controls. Qualitative as well as quantitative aspects of these distributions will be described. To complement this morphological data with a neurochemical correlate, GDNF levels in amygdalar tissues will be also be measured using a highly sensitive assay. Alterations documented in limbic regions of depressed and suicide brains are hypothesized to result from dysregulations in neurotrophin signaling. By providing the first comparative data on GDNF transmission in relation with dopaminergic afferents in the amygdala of depressed...
U.S. National Suicide Prevention Research Efforts: 2008-2013 Portfolio Analyses
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suicides and control subjects, this pilot study will pave the way to new research avenues in the neurobiology of suicide.

**Funding Organization:** American Foundation for Suicide Prevention  
**Study Title:** Childhood Trauma and Suicidal Behaviors: The Role of the Hypothalamic-Pituitary-Adrenal (HPA) Axis in Mediating Risk  
**Principal Investigator:** Holly Wilcox  
**Year When Study First Received Funding:** 2009  
**Abstract:** To study the role of Hypothalamic-Pituitary-Adrenal (HPA) axis dysfunction in mediating risk for suicidal behaviors among those exposed to childhood trauma. The potential pathway from childhood trauma to suicidal behaviors will be studied by assessing whether: 1) childhood trauma increases risk for HPA axis dysfunction and 2) whether HPA axis dysfunction increases risk for suicidal behaviors via increasing impulsive aggression. The aforementioned associations will be analyzed among offspring of adults enrolled in the Baltimore site of GenRED and GenRED II (Genetics of Recurrent Early-Onset Major Depressive Disorder). Elements of the proposed pathway to suicidal behavior will be elucidated and should constitute potential preventive and therapeutic targets.

**Funding Organization:** American Foundation for Suicide Prevention  
**Study Title:** A Prospective Study of Completed Suicide in a Large Bipolar I Disorder Sample  
**Principal Investigator:** William Coryell  
**Year When Study First Received Funding:** 2009  
**Abstract:** To identify clinically important risk factors for suicide in bipolar I disorder and to collect data necessary for genetic association studies of completed suicide. The investigators will collect the names and birthdates of individuals with bipolar I disorder identified in five successive waves conducted by the NIMH Genetics Initiative Bipolar Group. These will be submitted to a National Death Index search to identify those who have died and their causes of death. This outcome information will be added to the central data file and used to test hypotheses concerning relative risk factors for suicide in bipolar I disorder. Nearly all of the research into risk factors for suicide in the affective disorders has been conducted using groups that either mixed unipolar and bipolar subjects, or that were confined to major depressive disorder subjects. Recent evidence that the risk factors for suicide differ across groups with MDD, bipolar II, and bipolar I disorders indicates that the identification of risk factors peculiar to bipolar I disorder will better inform clinicians in their decisions regarding surveillance and intervention.

**Funding Organization:** American Foundation for Suicide Prevention  
**Study Title:** BDNF Promoter Methylation and Suicidal Behavior in Bipolar Disorder  
**Principal Investigator:** John Strauss  
**Year When Study First Received Funding:** 2010  
**Abstract:** This research grant will investigate methylation patterns in the brain-derived neurotrophic factor (BDNF) gene. Published research has reported that the BDNF gene and its products have been associated with suicidal behavior. Several lines of evidence point to BDNF as a factor in mood disorders and specifically bipolar disorder illnesses, where there are greater percentages of suicides or attempts. Epigenetic factors may play a
role and a mechanism for epigenetics is the modifications in gene expression that are controlled by heritable, but potentially reversible by changes in DNA methylation. Peripheral lymphocyte DNA methylation will be studied for genetic and epigenetic association with suicidal behavior. Two sources of variation at the BDNF locus will be analyzed: SNP variation (sequencing) and quantitative methylation using mass spectrometry. A subset of subjects of a genome-wide association study will be used for the lymphocyte samples. There will two sample groupings. Each will contain three separate subjects groups of 20 subjects each, for a total of 60 in both Sample I (bipolar depression with and without suicide attempts and matched health controls) and II (child-onset mood disorder bipolar depression prior to 17 years of age with and without suicide attempts and matched health controls). A deeper understanding of the genetic and neural substrates of behavior is essential for the next generation of preventive interventions, ranging from the role of biomarkers and endophenotypes in identifying those most in need of prevention to the longitudinal environmental sensitivity of neural systems.

**Funding Organization:** American Foundation for Suicide Prevention

**Study Title:** Differential microRNA Expression in the Prefrontal Cortex of Suicides

**Principal Investigator:** Gustavo Turecki

**Year When Study First Received Funding:** 2010

**Abstract:** This state-of-the-art genomic study will identify µRNA differences in prefrontal brain cortex of depressed suicides as compared to appropriate controls. µRNAs are non-coding, small, single stranded, 21-base RNA transcripts that play an important role in the posttranscriptional regulation messengerRNA (mRNA) thus playing a major role in the regulation of a large number of genes, including those expressed in the brain. A global profiling of expression patterns of µRNA levels in the orbital prefrontal cortex in 40 depressed suicide subjects and 40 psychiatrically normal controls will be done. The results of the global profiling analysis will be used for bioinformatics analysis to determine specific µRNA targets for validation, subsequent investigation and functional characterization. This study will facilitate our understanding of molecular mechanisms associated with the regulation of brain gene activity and how these mechanisms could be related to major depression and suicide. µRNA may, in fact, be an important regulating mechanism in the biological processes associated with suicide, and could lead to new biological markers, therapeutic targets and ultimately prevention.

**Funding Organization:** American Foundation for Suicide Prevention

**Study Title:** Number and Severity of Suicide Attempts: Relationship with Toxoplasma Gondii Anti

**Principal Investigator:** Teodor Postolache

**Year When Study First Received Funding:** 2010

**Abstract:** This preliminary case-control study is based on the hypothesis that Toxoplasma Gondii (the most common parasitic infection of the nervous system, which shifts between silent and micro-activated states) and the immune response that keeps the parasite in check may contribute to suicidal attempts in the presence of other vulnerabilities. The investigators preliminarily studies confirm an association between levels of antibodies to Toxoplasma and a history of attempting suicide in patients with recurrent mood disorders. In this current study bloods from healthy controls and patients with mental illness who either attempted or did not attempt suicide will be analyzed for Toxoplasma antibody levels. Considering the high prevalence and the neurotropism of Toxoplasma Gondii, confirming a role in predisposing or triggering suicidal attempts or exacerbating other suicide risk factors may have public health implications for treatment of mental illness and
suicide prevention. Success in finding a connection between *Toxoplasma Gondii* infections and attempting suicide will lead to a focus on behavioral, cellular and molecular mechanisms underlying the connection; expand to suicide completion and modeling suicide risk factors in animals; and design intervention trials in animals and then humans.

**Funding Organization:** American Foundation for Suicide Prevention  
**Study Title:** Genetic and Clinical Predictors of Suicidal Behavior in Veterans Returning from I  
**Principal Investigator:** Rachel Yehuda  
**Year When Study First Received Funding:** 2010  
**Abstract:** Recently deployed combat veterans serving in Operation Iraqi Freedom (OIF) in Iraq or Operation Enduring Freedom (OEF) in Afghanistan appear to be at high risk for attempted and completed suicide, but have not been formally characterized from a clinical or genetic perspective. Identification of clinical and gene markers for suicidal behavior (in consideration of co-morbid conditions such as PTSD and depression) in this group would contribute to efforts by the Department of Defense (DOD) and the Department of Veterans Affairs (VA) to more accurately identify persons at greater risk for suicide following combat trauma; this will help identify pathways that may be involved in suicide and, accordingly, the development of more effective strategies for prevention of suicide in this growing at risk population. The contribution of extreme stress experienced during deployment is thought to be a contributor to suicidal behavior raising the question of whether in combat veterans; there are additional markers of suicide other than those that have been associated with suicide in non-veterans (e.g., impulsivity, aggression). The study aim is to determine clinical and genetic/molecular risk factors for suicidal behavior in treatment-seeking combat veterans. The investigator will conduct a case control study of 120 treatment-seeking combat veterans expressing suicidal behavior (cases) compared to those who do not (controls). Half of the sample will have made a recent suicide attempt and cases will be matched to controls on age, gender, race/ethnicity and length of deployment. A single blood sample will be obtained in order to examine gene expression profiles using microarray analyses and quantitative polymerase chain reaction (qPCR) from RNA extracted from whole blood.

**Funding Organization:** American Foundation for Suicide Prevention  
**Study Title:** Investigation into the Role of Genes and Stress in Depression and Suicide among Medical Interns  
**Principal Investigator:** Srijan Sen  
**Year When Study First Received Funding:** 2010  
**Abstract:** The first aim of this study is to identify the factors involved in the development of suicide-related outcomes (SROs) and other mood symptoms among medical interns. A second is to investigate the interactions between genes and stress in the development of suicide. Medical internship is a time of high stress, characterized by sleep deprivation, extreme emotional situations and long work hours. This study will assess baseline psychiatric symptoms in subjects prior to the start of internship duties and then follow these subjects through the course of the intern year for the development of SROs and other depressive symptoms. DNA samples will be collected to investigate the interactions between specific genes and stress in the development of SROs. This project will contribute to suicide prevention by increasing the awareness among training physicians of the risk of SROs and depression, both for themselves and for their patients. It will also help us to understand the pathophysiology underlying suicide and mood disturbances in order to clarify the underlying biological mechanisms that will lead to better identification and treatment of at risk patients.
**Funding Organization:** American Foundation for Suicide Prevention  
**Study Title:** Investigation of Inheritance Patterns of Polymorphisms in Genes Regulating the Hypothalamic-Pituitary-Adrenal (HPA axis), in Relation to Suicidal Behavior and Its Endophenotypes  
**Principal Investigator:** Danuta Wasserman  
**Year When Study First Received Funding:** 2011  
**Abstract:** To help us better understand the underlying vulnerability towards suicidality at the level of individual variation in the genes involved in regulation of the stress-modulating “HPA-axis”, with the goal to increase and improve the options available for suicide prevention. Specific (combinations of) genetic variants in genes regulating one of the major stress-responsive neurosystems, the HPA axis, explain in part why certain individuals are susceptible towards performing suicidal acts (as well as displaying the endophenotypes thereof), in addition to, or by interaction with, the exposure to certain adverse life experiences. Identification of novel and verification of previously indicated genetic components of suicidality, holds the promise of delivering significant explanations as to why certain individuals are at risk for suicidality, as well as being seemingly necessary for the future improvement of current population-based interventions and clinical risk-assessment, as well as for construction of reliable diagnostic and treatment tools, respectively, having increased sensitivity and specificity for the suicidality aspect of the individual. Investigation of the predictive risk-assessment potential of the (combinations of) identified genetic variants for identifying suicidal individuals in the clinic, as well as using the novel genetic parameters in the design and analysis of outcomes of various public health interventions performed against suicide in the general population. More detailed studies of the neurobiological mechanism(s) involved with these variants, on the impact on intermediate (endo) phenotypes of suicidal behavior, opening the possibility for better causal understanding and increasing the possibilities in treatments by using drugs.

**Funding Organization:** American Foundation for Suicide Prevention  
**Study Title:** GABA System Genes and Suicidal Behavior in Psychiatric Disorders  
**Principal Investigator:** Clement Zai  
**Year When Study First Received Funding:** 2011  
**Abstract:** The key objectives of the proposed study are to investigate DNA polymorphisms in genes associated with the GABA neurotransmitter system for association with suicidal behavior, and to determine the potential functional significance of these polymorphisms. The applicant hypothesizes that selected GABA system genes will be associated with suicide risk, that DNA resequencing of these genes will reveal novel variants that will determine gene expression levels, and that combination of variants may interact to contribute to risk variants for suicide. This research will genotype SNPs across several GABAergic related genes, including GAD, the GABA transporter and three GABA receptor subunits. These genes were chosen based on previous associations with mood disorders. In addition, targeted multiplexed resequencing of the 10 kb region upstream of each of the five selected candidate genes will be conducted to identify variants within regions of these genes that might contribute to changes in gene expression. Two samples consist of bipolar patients and a third schizophrenics. One bipolar population has 352 subjects with 86 attempters, the second has 450 subjects and 122 attempters and the schizophrenic population has 231 subjects with 81 attempters. There are postmortem brain tissue samples from Brodmann’s area 46 (Stanley Foundation) from 41 schizophrenic subjects (10 suicide) and 44 bipolar subjects (22 suicide). In addition, the investigator plans access to additional schizophrenic, bipolar and depressed brain tissue from the Harvard Brain collection and the Stanley Foundation brain collection.
**Funding Organization:** American Foundation for Suicide Prevention  
**Study Title:** Identification of Neurophysiological Markers of Suicidal Behavior and Impulsivity  
**Principal Investigator:** Masoud Kamali  
**Year When Study First Received Funding:** 2011  
**Abstract:** The aims of this study are to compare neurophysiological measures of response inhibition in two groups of 20 bipolar subjects with and without a lifetime history of suicide attempts, and a group of 20 unaffected controls to identify a marker for suicidal behavior and to correlate that marker to other clinical measures of impulsivity. It is hypothesized that bipolar patients with a history of suicidality will exhibit deficits in a response inhibition task as indicated by smaller amplitude and delayed latency in two event relate brain potential (ERP) components (P300 & N200). The patient groups are to be matched by drug class of active medication. Patient subjects will be drawn from an existing pool of subjects participating in an ongoing high surveillance-intensity follow-up study. ERP deficits will reflect impaired impulse control and correlate with suicidal behavior and other clinical measures of impaired impulse control. This project hopes to identify markers of response inhibition in patients with a history of suicidality with the intention of better prediction of suicidal behavior in the future.

**Funding Organization:** American Foundation for Suicide Prevention  
**Study Title:** microRNAs in Postmortem Brain of Suicide Subjects  
**Principal Investigator:** Yogesh Dwivedi  
**Year When Study First Received Funding:** 2011  
**Abstract:** The hypothesis to be tested is that a subset of microRNAs (mRNAs) will show alterations in the brain of suicides and will be a part of the pathogenesis of suicide by targeting genes that regulate normal brain function. mRNAs are single stranded non-coding RNAs that are post-translational regulators. An individual mRNA can interact with several mRNAs and thus may regulate the expression of a family of functionally related genes. Each mRNA may silence hundreds of mRNAs. The study of mRNAs is a very new research area. There is emerging evidence that mRNAs contribute to risk of neuropsychiatric disorders, and that these brain disorders exhibit altered mRNA expression; more recently, it was shown that antidepressants regulate the expression of mRNAs in rat brain. Proteins such as CREB and BDNF, that are down-regulated in suicide, both are regulated and targeted by certain mRNAs. Therefore, mRNAs are likely to interact with known pathways involved in pathogenesis of neuropsychiatric diseases. This investigator will: test whether expression of mRNAs is altered in prefrontal cortex of suicide subjects; test whether the nucleotide sequences of mRNAs are specifically altered in suicide brain, by carrying out high through put deep sequencing; and identify predicted targets of altered mRNAs and examine whether mRNA levels of some of the predicted targets are altered in suicides. This proposed study will be performed in postmortem brain samples obtained from adult suicide subjects and matched non-psychiatric controls.
Funding Organization: American Foundation for Suicide Prevention
Study Title: Global Expression Analysis of Patients with Treatment Emergent Suicidal Ideations
Principal Investigator: Falk Lohoff
Year When Study First Received Funding: 2011
Abstract: Suicidal thoughts emerging during antidepressant treatment, while controversial, have led to black box warnings and concern about suicide risk in patients treated for major depression. Yet, little is known about the mechanism by which antidepressants might provoke suicidal thinking, at least in vulnerable patients. This proposal aims to address this issue. If successful, the project could shed light on mechanisms and nominate peripheral biomarkers that could be used to identify patients at high risk. The main objective of the grant is to determine differences in baseline and serotonin-induced global gene expression in lymphoblastoid cell lines from major depressive subjects that developed treatment emergent suicide ideation (TESI) relative to major depressive subjects that did not develop suicide ideation. All patient recruitment has been completed from the STAR*D trial and clinical as well as lymphoblastoid cell lines are available. Gene expression will be evaluated in 22 patients with MDD+TESI and 22 patients without MDD+TESI. Subjects will be matched for severity based on the HAM-D baseline scores, and for age, gender and family history of suicide.

Funding Organization: American Foundation for Suicide Prevention
Study Title: Copy Number Variation in Suicide
Principal Investigator: Carl Ernst
Year When Study First Received Funding: 2011
Abstract: Dr. Ernst is working to identify genetic risk factors for suicide by studying changes in gene structures known as copy number variations (CNV). DNA or gene structures vary from person to person as genes copy themselves. Over time, imperfections in this process, known as "disruptions," can lead to large losses or increases in DNA. CNVs have been shown to be important, although uncommon, sources of risk for some psychiatric disorders. Dr. Ernst will examine the relationship between CNVs and suicide risk among individuals with bipolar and unipolar depression by comparing individuals with a history of suicide attempts and individuals without a history of a suicide attempt. His hypothesis is that those with a history of a suicide attempt will carry CNVs with 1) more disrupted genes; 2) larger disruptions; and 3) more possible problems in the way the genes are interpreted in the brain. In addition, he will examine whether CNV disruptions found in people who have made suicide attempts are also found in people who died by suicide. The mentorship goal is to develop skills to understand the genetic risk for suicide, with an emphasis on the association between CNVs and suicide.

Funding Organization: American Foundation for Suicide Prevention
Study Title: Functional Analyses of Differential DNA Methylation in Frontal Cortex of Suicide
Principal Investigator: Gilles Maussion
Year When Study First Received Funding: 2012
Abstract: DNA methylation is the normal process through which genes are turned on or turned off during the early stages of development. Dr. Maussion will use his fellowship to study the methylation of a specific gene, the TrkB receptor, a gene that has been found to be related to suicide by his mentor, Dr. Turecki. TrkB plays a critical role in the development of the nerves, synapses, and the messaging system of the brain. In his study,
Dr. Maussion will characterize the TrkB receptor gene DNA sequence in the frontal cortex of the brain by studying 40 men who had major depression and died by suicide and comparing them with a group of 40 men who did not have major depression and died of other causes. He will also examine the expression of the TrkB receptor gene in other parts of the brain in comparison with the frontal cortex. He expects to find that variations in methylation impact the expression of TrkB and partially account for the lower levels found in suicide.

**Funding Organization:** American Foundation for Suicide Prevention  
**Study Title:** Familial Risk for Suicide and Self-Injury: Testing Theories in Multigenerational  
**Principal Investigator:** Sheila Crowell  
**Year When Study First Received Funding:** 2012  
**Abstract:** Completed suicide is relatively infrequent and large samples are needed for informative family genetic studies of suicide. Because of this, the first recommendation in the Institute of Medicine’s report on suicide was for the National Institutes of Health (NIH) to develop and support a national network of suicide research Population Laboratories devoted to interdisciplinary research on suicide and suicide prevention across the life cycle." The University of Utah houses the Utah Population Database (UPDB), a unique database that contains linked, de-identified medical, census, birth/death, marriage/divorce, driver’s license, and demographic records on over seven million individuals dating from 1750 to the present. The goal of this pilot study is to lay the foundation for a sustained research program of population-level suicide research. Dr. Crowell’s study has two primary aims: (1) to construct high risk family trees or pedigrees of families with multiple suicides, and (2) to examine the relative risk for suicide and intentional, non-fatal self-injury within those family trees in comparison with families without suicidal behavior. She hypothesizes that rates of suicide and self-injury will be elevated within high-risk pedigrees relative to case-matched controls. The establishment of this database will provide a national resource that can be linked with other public databases for studying suicide and suicidal behavior.

**Funding Organization:** American Foundation for Suicide Prevention  
**Study Title:** Modeling 5-HT1A Receptor Transduction Pathways in Suicide  
**Principal Investigator:** Thomas Franke  
**Year When Study First Received Funding:** 2012  
**Abstract:** Chronic stress has been found to affect the biochemistry of the brain. Some types of changes are in the serotonin system and have been identified in post-mortem brain studies of depressed individuals who have died by suicide. Akt is one such serotonin related brain chemical. Dr. Franke will use his grant to try to recreate, in genetically modified mice, the brain changes in the Akt protein that have been found in post-mortem studies of depressed suicide victims. He will use a behavioral model of depression in mice that is based on a chronic stress model. He will test the importance and relevance of brain and behavioral changes to depression and suicide, as well as to resilience and resistance, when confronted with chronic stress.
**Funding Organization:** American Foundation for Suicide Prevention  
**Study Title:** Optical Brain Imaging Predictors of Treatment Response to Dialectical Behaviour Therapy for Non-suicidal Self-injury in Borderline Personality Disorder  
**Principal Investigator:** Anthony Ruocco  
**Year When Study First Received Funding:** 2012  
**Abstract:** The reduction of non-suicidal self-injury (NSSI) is a key target of Dialectical Behavior Therapy (DBT) for patients with borderline personality disorder (BPD). The identification of biological indicators of treatment response for NSSI in BPD is an important unmet need that has significant ramifications for optimizing treatments to reduce NSSI among these patients. Impulsivity has been identified as an essential feature of BPD that places patients at an increased risk for NSSI and suicide completion. Neuroimaging studies of impulse control, or response inhibition, implicate the ventrolateral prefrontal cortex (VLPFC) of the brain as a critical behavioral control center for BPD patients, who show reduced activation of this region under conditions of response inhibition; that is, not acting when identifying a stimulus. Activation of the VLPFC may thus serve as a promising biological indicator of treatment-associated changes in NSSI for patients with BPD. Dr. Ruocco will evaluate activation of the VLPFC on tests of response inhibition as a possible predictor of treatment response in this high-risk group. Thirty-one outpatients with BPD and NSSI from the Centre for Addiction and Mental Health in Toronto, Canada, will be evaluated prior to and after completing six months of DBT, Patients will complete tests of response inhibition (go/no-go and stop-signal tasks) while functional activation of the VLPFC is monitored using near-infrared spectroscopy. He will test whether VLPFC activation is associated with NSSI outcome measures. This research has the potential to identify biological markers that could predict which BPD patients may be most responsive to a psychological treatment aimed at reducing NSSI.

**Funding Organization:** Brain & Behavior Research Foundation  
**Study Title:** Suicidality in Major Psychoses: Methylation Analysis Based on Genomic Imprinting  
**Principal Investigator:** Vincenzo De Luca  
**Year When Study First Received Funding:** 2008  
**Abstract:** Vincenzo De Luca, M.D., of Centre for Addiction and Mental Health/University of Toronto, aims to identify genetic (polymorphism) and epigenetic (gene methylation) predictors of increased suicide risk in psychiatric patients with chronic mental illness (the most common diagnoses include schizophrenia and bipolar disorder). Suicide has been noted to be familial in many cases, and subjects with schizophrenia and bipolar disorder have a high rate of suicide attempts. The genetic risk markers for suicide that this study could, in the future, identify persons at risk and thus facilitate preventive measures such as counseling, family education, and early treatment intervention for these individuals. Furthermore, the identified genes may reveal new neurobiological mechanisms in suicide that may be used as targets for development of novel medications to prevent suicide.
**Funding Organization:** Brain & Behavior Research Foundation  
**Study Title:** The Neuropeptide Galanin and Its Receptors  
**Principal Investigator:** Tomas Hokfelt  
**Year When Study First Received Funding:** 2009  
**Abstract:** Tomas Hokfelt, M.D., Ph.D., of Karolinska Institute, is studying several neuropeptide receptors, including those of galanin, which represent targets for development of a new class of antidepressant drugs. Neuropeptides represent the largest group of messenger molecules in the brain, almost always representing co-transmitters. They act via 7-transmembrane, G-protein coupled receptors (GPCRs) and are potential targets for drug development. The focus in this project is on galanin and its three receptors, GalR1-R3. In rat, galanin is coexpressed in the noradrenaline (NA) neurons in the locus coeruleus (LC) and in the serotonin neurons in the dorsal raphe nucleus (DRN). A number of animal studies suggest that a galanin antagonist could have an antidepressant effect, a theory strongly supported by the recent demonstration that small-molecule GalR3 antagonists have antidepressant and anxiolytic action in several rat models. The question to be addressed in this study is the extent to which the galanin system shown in rodents also exists in the human brain, and whether promising results with galanin antagonists in animal models might apply in humans.

**Funding Organization:** Brain & Behavior Research Foundation  
**Study Title:** Interaction between the Glutamatergic and Serotonergic Systems in Suicide in Mood  
**Principal Investigator:** Adolfo Sequeira  
**Year When Study First Received Funding:** 2010  
**Abstract:** Adolfo Sequeira, Ph.D., of the University of California, Irvine, proposes that understanding the gene expression changes associated with suicide in mood disorder subjects should improve suicide intervention and prevention efforts. He wants to study whether and how key genes affecting glutamate and serotonin receptors are implicated in mood disorders and suicide. He will be part of a team focusing on gene expression three regions, the dorsolateral prefrontal cortex (DLPFC), the amygdala and the nucleus accumbens. In order to explore the specific involvement of those genes in suicide and/or mood disorders, a cohort of mood disorder patients and a cohort of normal controls will be utilized. The ultimate goal is a specific brain-biological signature of suicidal behavior and of mood disorders.

**Funding Organization:** Brain & Behavior Research Foundation  
**Study Title:** Suicide and Obesity a Curious Association  
**Principal Investigator:** Zainab Samaan  
**Year When Study First Received Funding:** 2012  
**Abstract:** Zainab Samaan, M.D., of McMaster University, Canada, is interested in probing the association, if any, between obesity and the risk of suicide in an individual. It is known that obesity is associated with depression, and depression is in turn a risk factor for suicide; yet obesity has been cited as a 'protective' or mitigating factor in suicide risk. Samaan hypothesizes this is explained by high levels of cholesterol in the blood. Obesity is associated with high levels of cholesterol, and cholesterol is an important substance in the brain. 60% of our brains are made of lipids including cholesterol that is essential for normal brain function such as transmission of brain cells signals. Some studies also show that low cholesterol might be associated with suicide and low serotonin levels. The current project will investigate the association between suicide...
attempts and obesity (using body mass index or BMI as the measure of obesity) and test if this association holds up when one controls for the presence of confounding variables such as psychiatric diagnosis, medical illness and life style factors such as diet and physical activity. The team also plans to test the association between cholesterol blood level and suicide attempts and for the effect of cholesterol on the relation between obesity and suicide.

**Funding Organization:** Brain & Behavior Research Foundation  
**Study Title:** Genetics of Suicidal Behaviour: Genome-wide Association Study and Targeted Resequencing  
**Principal Investigator:** Clement C. Zai  
**Year When Study First Received Funding:** 2012  
**Abstract:** Clement C. Zai, Ph.D., of the Centre for Addiction and Mental Health at the University of Toronto, is studying possible genetic linkages with suicidal behavior. He notes that suicides tend to run in families, and that 90% of victims suffered at least one psychiatric disorder. His team seeks to identify identifying novel DNA variants across the human genome in archival samples of chronic schizophrenia/bipolar disorder patients (sample size>1,000), and then compare the frequency distributions of the genotypes and alleles of these polymorphisms between patients with and without lifetime history of suicidal attempts. By sequencing of regions around significant DNA variants Zai will provide extensive information at the DNA level that could identify novel variants for further study. The ultimate aim of the research is to generate information that would permit screening of people at risk.

**Funding Organization:** Brain & Behavior Research Foundation  
**Study Title:** Identification and Characterization of Transcriptional Regulators Mediating the Relationship between Early Childhood Adversity and Development of Psychopathology Later in Life  
**Principal Investigator:** Laura Marie Fiori  
**Year When Study First Received Funding:** 2013  
**Abstract:** Mental illnesses are debilitating and often chronic conditions whose development and pathology result from the interaction of a variety of clinical, social, genetic, and environmental factors. In recent years, the importance of early life stressors in the development of psychiatric disorders has become increasingly recognized. Numerous efforts are currently being undertaken to identify the biological mechanisms by which the early environment can interact with the genome to produce long-term neurobiological alterations. One method by which this is believed to occur is through the epigenetic process known as DNA methylation, which can occur at specific sites in the DNA, and yield stable changes to gene expression. The aim of the present study is to investigate the functional relationship between gene expression and specific DNA methylation marks which have been found to be associated with early childhood adversity and the development of psychopathology later in life. To this end, we will first use reporter gene assays to assess the effects of DNA methylation at these sites on gene expression. We will then use a combination of bioinformatics, electromobility shift assays, and yeast one-hybrid assays, to identify transcription factors whose binding abilities at these sites are affected by the presence of DNA methylation. Subsequently, reporter gene assays will be used to confirm transcription factor binding and examine their effects on gene expression in vitro. Finally, chromatin immunoprecipitation assays will allow us to confirm the existence of transcription factor-DNA complexes in cell culture, as well as to identify the presence of specific post-translational histone modifications: another important epigenetic process which has been implicated in mental illness. Overall,
these studies will allow us to elucidate specific molecular mechanisms by which epigenetic changes which occur early in development are capable of yielding long-term changes to gene expression. Ultimately, these processes represent novel targets for both early diagnosis and psychopharmacological treatment of mental disorders.

**Funding Organization:** Centers for Disease Control and Prevention  
**Study Title:** Developmental Pathways to Dating Violence and Suicidal Behavior: The Healthy Teen  
**Principal Investigator:** Pamela Orpinas  
**Year When Study First Received Funding:** 2008  
**Abstract:** The goal of Healthy Teens is to increase scientific understanding of different levels of risk and protective factors that influence the developmental pathways (i.e., patterns of continuity or patterns of change over time) that children and young adolescents follow from 6th through 12th grade, in relation to dating violence and suicidal thoughts and behaviors. Healthy Teens differs from much of the extant research literature in that it: a) is a longitudinal study of a large sample (cohort of approximately 700 students); b) uses multiple methods (student surveys, teacher ratings, archival data on academic achievement and discipline, focus groups, and interviews; c) includes two samples of students (random and high risk); d) evaluates a large number of violence related constructs and behaviors, including risk and protective factors at multiple levels of an ecological framework; and e) includes students who dropped out of school. The unique, comprehensive design of Healthy Teens will serve to enhance our comprehension of the development of dating violence and its interrelation with suicidal thoughts and behaviors and, thus, provide a firm foundation to enhance prevention strategies. Objectives: Specific objectives are to: a) evaluate developmental trajectories from middle to high school in relation to dating and dating violence victimization and perpetration and its interrelation to suicidal thoughts and behaviors; b) evaluate the risk and protective factors that influence these developmental trajectories; and c) explore the context and meaning of dating violence from students’ perspectives. Study Design: Healthy Teens is a mixed method study that began when students were in the 6th grade; they are currently in the 11th grade. This study proposes to complete one more year of data collection (12th grade—“Year 1”) so that that there will be complete, comprehensive data set of this cohort from middle through high school. Data analyses will be conducted during Years 1, 2 and 3 of the proposed study. This study will employ the same data collection strategies used since students were in the 6th grade, that is: a) student self-reported assessments; b) teacher behavioral ratings of students (BASC); and c) archival data. Additionally, individual interviews will be conducted with a purposeful, maximum variation sample of students who have been victims and/or perpetrators of dating violence. Setting: Healthy Teens researchers will work cooperatively with school administration and staff to collect data in the schools, as in years past. When this is not possible (e.g., student who has dropped out of school), data will be collected in students’ homes or another convenient location (e.g., public library). Participants: Healthy Teens has followed a cohort of approximately 700 students (currently in the 11th grade) in eight Northeast Georgia high schools. When students were in the 6th grade (9 middle schools), two types of samples were recruited: a random sample and a high risk for aggression sample. The random sample (676 students) represented the student population of each school; the high risk sample (213 students) consisted of students who were considered by their teachers to be aggressive and influential with peers. A small number of students (107) in the random sample were also selected for the high risk sample. Outcome Measures: All students have completed questions on dating violence norms, dating, and dating violence behaviors; high school students have completed questions related to feelings of sadness and hopelessness and suicidal thoughts and attempts. In addition, all students have
completed an array of measures of risk and protective factors at the individual, family, peer, and school levels. Census data on individual neighborhood characteristics are also available.

**Funding Organization:** Department of Defense  
**Study Title:** U.S. Army-National Institute of Mental Health Study to Assess Risk and Resilience in Service Members (Army STARRS)  
**Principal Investigator:** Bob Ursano  
**Year When Study First Received Funding:** 2009  
**Abstract:** This proposal is submitted in response to RFA-MH-09-140 by an interdisciplinary team from four institutions: the Uniformed Services University of the Health Sciences (USUHS), Harvard Medical School (HMS), the University of Michigan (UM), and Columbia University (CU). The team has unparalleled expertise in research on military mental health (USUHS), general population psychiatric epidemiology (HMS), large-scale epidemiological data collection (UM), and neurobiological-clinical research on suicidal behaviors (CU). We propose a multi-phase epidemiological study that considers diverse psychosocial and neurobiological risk and protective factors for suicidal behaviors and secondary outcomes in order to make evidence-based recommendations for implementation of Army suicide prevention interventions. An enriched version of the Army Suicide Event Report (ASER) system will be developed to define the primary outcomes incorporating information from the DoD Medical Mortality Registry (MMR) and Total Army Injury and Health Outcomes Database (TAIHOD). Our study design will include both a retrospective case-control component for quickefficient hypothesis testing and a prospective survey component to predict subsequent suicidal behaviors and secondary outcomes (onset, persistence, worsening of DSM-IV disorders, suicide ideation, suicide plans). We will also use data from the ongoing Pre- and Post-Deployment Health Reassessment Program (PDHRP) surveys as secondary outcomes. The case-control survey will study soldiers who made nonfatal attempts and relatives of soldiers who committed suicide in a psychological autopsy framework. Parallel data will be collected from carefully matched controls. Blood samples and, in the case of nonfatal attempters and their controls, saliva samples will be collected to allow neurobiological risk and protective factors to be studied. The survey component will include active duty personnel across all phases of Army service. Survey reports will be linked to subsequent ASER records and PDHRP reports to study prospective associations of predictors with suicidal behaviors and secondary outcomes. A number of innovative measurement, design and analysis features will be used to increase chances of discovering effective intervention possibilities.

**Funding Organization:** Department of Defense  
**Study Title:** Neuroimaging Correlates of Suicide Risk  
**Principal Investigator:** Deborah Yurgelun-Todd  
**Year When Study First Received Funding:** 2013  
**Abstract:** Brain changes have been implicated in self-directed violence in returning service men and women. Additional information on neurobiologic changes that may be associated with risk for self-directed violence is needed in order to develop improved intervention and treatment strategies. We hypothesize that Veterans with a history of self-directed violence as evaluated by MSRC gold standard assessments will show significant differences in frontal frontal imaging endpoints. We also hypothesize that significant associations will be
present between MR indices and measures of suicidal ideation, suicide intent and suicidal and non-suicidal self-injury.

**Funding Organization:** National Institutes of Health  
**Study Title:** Immune System Activation in Adolescent Suicide  
**Principal Investigator:** Vilma Gabbay  
**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. This protocol is designed to test the hypothesis that there is immune system activation in suicidally depressed adolescents, as reflected by higher Th1-type immunologic responses (cells and cytokines) than in non-suicidally depressed adolescents or age- and sex-matched controls. This is based on prior observations on the effect of serotonin and dopamine receptors and their dysfunction in depression and in the immune system. 20 suicide-attempt (within the past 10 days) adolescents will be recruited and compared to 20 depressed adolescents and 20 "normal" adolescents. The first aim is to measure a series of cytokines: IFNg, TNFa and IL-2 (Th1) vs IL-4 and IL-6. In addition, quantitation of intracellular cytokines will give an indication of Th1 or Th2 type cells in the peripheral blood following stimulation. All of the subjects will also undergo a series of standardized tests for depression. The patient groups will be as above, with exclusions for medication, infections, immunologic or hematologic disorders.

**Funding Organization:** National Institutes of Health  
**Study Title:** 5-HT1A Receptor Anti-apoptotic Transduction Pathways in Suicide  
**Principal Investigator:** Victoria Arango  
**Year When Study First Received Funding:** 2008  
**Abstract:** DESCRIPTION (provided by applicant): The 5-HT1A receptor is implicated in the pathology of anxiety, major depression and suicide. Studies with mutant mice indicate that the 5-HT1A receptor is necessary for the long-term viability of brain networks. Preliminary studies suggest that the activation of signaling molecules downstream of the 5-HT1A receptor is attenuated in the occipital cortex (OC) of suicides. We will determine whether this attenuation of signal transduction pathways is a characteristic of major depression or related to the diathesis for suicide by comparing suicides with major depression (MDD) to suicides with schizophrenia (SZ) and to nonpsychiatric, nonsuicide controls. We will evaluate four brain regions, one where we have found changes in both major depression and suicide (ventral prefrontal cortex, vPFC) and three regions where the findings seem more specifically linked to major depression (anterior cingulate cortex [ACC], dorsolateral PFC [BA9] and hippocampus). We predict signal transduction effects related to suicide will be present in both suicide groups and confined to the vPFC. We would predict the signal transduction changes related to MDD will be found in the MDD suicide group and not the other two groups and in the ACC and dorsal prefrontal cortex. We will test the hypothesis that 5-HT1A receptor-activated transduction pathways linked to cell survival are downregulated in specific brain regions relevant to major depression or for suicide. We will measure signaling proteins downstream of 5-HT1A receptors that are regulated via coupling to Gi/o and Gsubunits. One pathway involves the Gai-mediated inhibition of adenylyl cyclase (AC) and protein kinase A.
The 5-HT-dependent inhibition of AC is normally counterbalanced by the concomitant activation of cell survival pathways. We propose that the reduced inhibition of AC in suicides represents a mechanism to counteract the reduction in the activity of the transduction pathways activated via the Gbg subunit. Investigating 5-HT1A receptor activation of NFkB, PI3-K/Akt and ERKs in suicide will advance our understanding of the role of 5-HT1A receptor signal pathways in depression and suicidal behavior. The cerebellar hemisphere will serve as a control region. We will also measure neuronal density, the levels of pro-apoptotic signaling molecules and death effectors. We hypothesize that the viability or functionality of brain cells that express 5-HT1A receptors is neuroendangered in major depression or suicide. Unraveling these events biochemically will yield crucial insights into the neurobiology of depression and suicide, major mental health problems in the US and the world. It may also identify novel drug targets for the treatment of depression and for the prevention of suicide.

PUBLIC HEALTH RELEVANCE: Suicidal behavior is a major health problem in the United States and the world. With 30,000 deaths by suicide per year in the US, suicide is the 11th leading cause of death. We have data indicating that the neuroprotective cellular pathways associated with the serotonin 1A receptor are altered in suicide. We want to explore this further by studying these pathways in various brain regions of suicides (depressed and schizophrenic) and normal controls. We hope to gain insight into the neurobiology of suicide versus depression and identify novel drug targets for treatment of depression and prevention of suicide.

Funding Organization: National Institutes of Health
Study Title: Neuroimaging of Fatty Acids in Major Depression
Principal Investigator: M. Sublette
Year When Study First Received Funding: 2008
Abstract: DESCRIPTION (provided by applicant): The applicant is seeking to become an independent investigator focusing on the role of dietary essential polyunsaturated fatty acids (PUFAs) in the neurobiology of mood disorders and suicide, using positron emission tomography (PET). PROJECT DESIGN: Background.-PUFAs are implicated in mood disorders: 1) Low plasma levels of omega-3 PUFAs and higher ratios of omega-6 to omega-3 PUFAs have been found among depressed patients, and our pilot study suggests these indices predict suicide attempts. 2) Double-blinded, placebo-controlled studies have found that adding omega-3 fatty acids (fish oil) to standard treatment of depression improves outcomes in Major Depressive and Bipolar Disorders. 3) We find that similar brain regions have low glucose uptake among suicide attempters and in depressed patients with low fatty acids. Hypothesis: A functional imbalance between omega-3 and omega-6 PUFAs contributes to depression and suicidality. The objective is to clarify relationships between plasma PUFA levels, clinical characteristics, including suicide risk, and regional cerebral rates of glucose metabolism (rCMRglu) in Major Depressive Disorder. Aim1. In regions of interest (ROIs), test the following hypotheses: a) Lower rCMRglu correlates with lower plasma PUFAs in depressed subjects b). rCMRglu are lower in suicide attempters vs. non-attempters. Aim 2. Perform voxel-level analyses on rCMRglu and plasma PUFA levels in: a) Depressed subjects vs. healthy volunteers, b) Depressed subjects with and without suicide attempt history. Aim 3. Perform voxel-level analyses of effects of augmentation treatment with fish oil on rCMRglu, plasma PUFA levels, symptom severity, and the relationships between them. Aim 4. Characterize the effects of fish oil on plasma PUFAs and clinical status: a) Test the hypothesis that plasma levels of DMA will be lower in depressed subjects than healthy volunteers, and lower in suicide attempters than nonattempters. b) Assess overall clinical status and severity of individual symptoms. Methods: Thirty subjects with Major Depressive Disorder (half with history of suicide attempt) not responding to treatment and 15 healthy volunteers will
have quantitative PET scanning with [18F]FDG before and after adjunctive treatment for 4-6 weeks with fish oil. We will perform group comparisons of rCMRglu in ROIs and use statistical parametric mapping at the voxel level to generate difference and correlational maps. TRAINING: The candidate proposes to undertake specialized studies in neuroimaging methodologies, statistics, and lipid biochemistry. PUBLIC HEALTH RELEVANCE: Major Depressive Disorder and suicide are major public health problems worldwide. This study is expected to contribute to understanding the neurobiology of depression and may provide new information relevant to treatment with dietary fatty acids.

Funding Organization: National Institutes of Health
Study Title: Suicidal Behavior in Mood Disorders: Genes and Intermediate Phenotypes
Principal Investigator: Joseph Mann
Year When Study First Received Funding: 2008
Abstract: DESCRIPTION (provided by applicant): This collaborative R01 involves three sites: New York State Psychiatric Institute/Research Foundation for Mental Hygiene, Inc., in New York City, USA (Mann), McGill University in Montreal, Canada (Turecki) and University of Munich, Germany (Rujescu) to examine the complex genetic basis of suicidal behavior. We have contributed to the original observations showing that suicide and nonfatal suicide attempts have biologic changes that are distinct from those of major psychiatric disorders that underlie suicide such as major depressive disorder or bipolar disorder. We have reported candidate gene associations that are independently associated with mood disorders or with suicide attempts. We believe the field is ready for a major effort to survey the genome to seek genes associated with suicidal behavior that are independent of the major psychiatric illnesses. We have developed and tested a potential predictive stress-diathesis model of suicidal behavior derived from a comprehensive assessment of risk factors. Depressed individuals with prominent (1) pessimism and (2) severity of life-time aggression/impulsivity are at greater risk for suicidal behavior and the effects are additive. These clinical phenotypic components can be measured in the field in patients and suicides. We now propose to use genome-wide screens to identify candidate genes and conserved haplotype blocks within those genes 4000 cases that span the higher severity range of suicidal behavior, namely completed suicide and attempted suicide compared to both psychiatrically matched controls and to healthy volunteers. We have data on Axis I and Axis II diagnoses and data on lifetime aggression scores and current severity of depression to permit assessment of these potential etiological factors and potential behavioral endophenotypes. We have data on childhood reported histories of physical or sexual abuse which will be a focus for an exploratory gene-early environment interaction analysis. Causal SNPs will be further identified by sequencing the most promising gene segments. PUBLIC HEALTH RELEVANCE: The predisposition to suicidal behavior is substantially determined by genetic factors independent of those associated with major psychiatric disorders. This study will screen the genome in the largest collection of samples ever assembled for such a study of suicidal behavior in order to identify the responsible genes.
U.S. National Suicide Prevention Research Efforts: 2008-2013 Portfolio Analyses
Short-Term Research Objective 1.B.

**Funding Organization:** National Institutes of Health  
**Study Title:** Suicidal Behavior in Mood Disorders: Genes and Intermediate Phenotypes  
**Principal Investigator:** Dan Rujescu  
**Fiscal Year When Study First Received Funding:** 2008  
**Abstract:** DESCRIPTION (provided by applicant): This collaborative R01 involves three sites: New York State Psychiatric Institute/Research Foundation for Mental Hygiene, Inc., in New York City, USA (Mann), McGill University in Montreal, Canada (Turecki) and University of Munich, Germany (Rujescu) to examine the complex genetic basis of suicidal behavior. We have contributed to the original observations showing that suicide and nonfatal suicide attempts have biologic changes that are distinct from those of major psychiatric disorders that underlie suicide such as major depressive disorder or bipolar disorder. We have reported candidate gene associations that are independently associated with mood disorders or with suicide attempts. We believe the field is ready for a major effort to survey the genome to seek genes associated with suicidal behavior that are independent of the major psychiatric illnesses. We have developed and tested a potential predictive stress-diathesis model of suicidal behavior derived from a comprehensive assessment of risk factors. Depressed individuals with prominent (1) pessimism and (2) severity of life-time aggression/impulsivity are at greater risk for suicidal behavior and the effects are additive. These clinical phenotypic components can be measured in the field in patients and suicides. We now propose to use genome-wide screens to identify candidate genes and conserved haplotype blocks within those genes 4000 cases that span the higher severity range of suicidal behavior, namely completed suicide and attempted suicide compared to both psychiatrically matched controls and to healthy volunteers. We have data on Axis I and Axis II diagnoses and data on lifetime aggression scores and current severity of depression to permit assessment of these potential etiological factors and potential behavioral endophenotypes. We have data on childhood reported histories of physical or sexual abuse which will be a focus for an exploratory gene-early environment interaction analysis. Causal SNPs will be further identified by sequencing the most promising gene segments. PUBLIC HEALTH RELEVANCE: The predisposition to suicidal behavior is substantially determined by genetic factors independent of those associated with major psychiatric disorders. This study will screen the genome in the largest collection of samples ever assembled for such a study of suicidal behavior in order to identify the responsible genes.

**Funding Organization:** National Institutes of Health  
**Study Title:** Suicidal Behavior in Mood Disorders: Genes and Intermediate Phenotypes  
**Principal Investigator:** Gustavo Turecki  
**Year When Study First Received Funding:** 2008  
**Abstract:** DESCRIPTION (provided by applicant): This collaborative R01 involves three sites: New York State Psychiatric Institute/Research Foundation for Mental Hygiene, Inc., in New York City, USA (Mann), McGill University in Montreal, Canada (Turecki) and University of Munich, Germany (Rujescu) to examine the complex genetic basis of suicidal behavior. We have contributed to the original observations showing that suicide and nonfatal suicide attempts have biologic changes that are distinct from those of major psychiatric disorders that underlie suicide such as major depressive disorder or bipolar disorder. We have reported candidate gene associations that are independently associated with mood disorders or with suicide attempts. We believe the field is ready for a major effort to survey the genome to seek genes associated with suicidal behavior that are independent of the major psychiatric illnesses. We have developed and tested a potential
predictive stress-diathesis model of suicidal behavior derived from a comprehensive assessment of risk factors. Depressed individuals with prominent (1) pessimism and (2) severity of life-time aggression/impulsivity are at greater risk for suicidal behavior and the effects are additive. These clinical phenotypic components can be measured in the field in patients and suicides. We now propose to use genome-wide screens to identify candidate genes and conserved haplotype blocks within those genes 4000 cases that span the higher severity range of suicidal behavior, namely completed suicide and attempted suicide compared to both psychiatrically matched controls and to healthy volunteers. We have data on Axis I and Axis II diagnoses and data on lifetime aggression scores and current severity of depression to permit assessment of these potential etiological factors and potential behavioral endophenotypes. We have data on childhood reported histories of physical or sexual abuse which will be a focus for an exploratory gene-early environment interaction analysis. Causal SNPs will be further identified by sequencing the most promising gene segments. PUBLIC HEALTH RELEVANCE: The predisposition to suicidal behavior is substantially determined by genetic factors independent of those associated with major psychiatric disorders. This study will screen the genome in the largest collection of samples ever assembled for such a study of suicidal behavior in order to identify the responsible genes.

Funding Organization: National Institutes of Health
Study Title: Molecular Characterization of a Corticolimbic Network in Depression
Principal Investigator: Etienne Sibille
Year When Study First Received Funding: 2009
Abstract: DESCRIPTION (provided by applicant): Despite the substantial personal and economic burden of mood disorders, understanding the pathological and molecular features of these disorders remains a considerable challenge in psychiatric research. Dysregulated serotonergic and stress pathways appear to be contributing factors in major depression; however, it is likely that numerous other unidentified risk factors exist. Here we propose to investigate the molecular pathology of major depression, using a combined approach of microarray experiments, bioinformatic analysis and anatomical characterization of results. Our central hypothesis states that the biological liability to major depression is reflected in a persistent molecular pathology that is detectable in the postmortem human brain and that affects a cortico-limbic network, whose dysfunction might specifically cause, or at least correlate with, the affective component of depression. Hence, based on microanatomical and functional studies, we will concentrate on two densely interconnected brain areas within this cortical-limbic network of mood regulation: i) the amygdala (AMY), as a brain region that is crucial to the integration and expression of emotions, and ii) the anterior cingulate cortex (ACC), as depression-related functional and morphological changes have been consistently reported in this brain area. As microanatomical studies suggest a glial depression-related pathology in these two brain areas, we will apply novel analytical approaches to separately assess the contribution of altered glial or neuronal functions within the gray matter in correlation with major depression. Together, results from this research proposal could reveal either a general pathway that is common among all depressed subjects and/or specific pathways that may differ as a function of sex and family history of major depression, two factors that are associated with different phenotypic features of depression. The characterization of patterns of nuclei (AMY) and laminar (ACC) changes for selected genes will provide anatomical information to generate network-based hypotheses on the molecular pathology of depression. PUBLIC HEALTH RELEVANCE: The overall goal will be to assess causality of altered biological pathways or cellular mechanisms in the pathophysiology of major depression, as an essential step in identifying potential leads for novel therapeutic intervention in major depression.
Funding Organization: National Institutes of Health
Study Title: Modifiable Risk and Protective Factors for Suicidal Behaviors in the US Army
Principal Investigator: Robert J. Ursano
Year When Study First Received Funding: 2009
Abstract: DESCRIPTION (provided by applicant): This application is submitted in response to RFA-MH-09-140 by an interdisciplinary team from four institutions: the Uniformed Services University of the Health Sciences (USUHS), Harvard Medical School (HMS), the University of Michigan (UM), and Columbia University (CU). The team has unparalleled expertise in research on military mental health (USUHS), general population psychiatric epidemiology (HMS), large-scale epidemiological data collection (UM), and neurobiological-clinical research on suicidal behaviors (CU). We propose a multi-phase epidemiological study that considers diverse psychosocial and neurobiological risk and protective factors for suicidal behaviors and secondary outcomes in order to make evidence-based recommendations for implementation of Army suicide prevention interventions. An enriched version of the Army Suicide Event Report (ASER) system will be developed to define the primary outcomes incorporating information from the DoD Medical Mortality Registry (MMR) and Total Army Injury and Health Outcomes Database (TAIHOD). Our study design will include both a retrospective case-control component for quick efficient hypothesis testing and a prospective survey component to predict subsequent suicidal behaviors and secondary outcomes (onset, persistence, worsening of DSM-IV disorders, suicide ideation, suicide plans). We will also use data from the ongoing Pre- and Post-Deployment Health Reassessment Program (PDHRP) surveys as secondary outcomes. The case-control survey will study soldiers who made nonfatal attempts and relatives of soldiers who committed suicide in a psychological autopsy framework. Parallel data will be collected from carefully matched controls. Blood samples and, in the case of nonfatal attempters and their controls, saliva samples will be collected to allow neurobiological risk and protective factors to be studied. The survey component will include active duty personnel across all phases of Army service. Survey reports will be link to subsequent ASER records and PDHRP reports to study prospective associations of predictors with suicidal behaviors and secondary outcomes. A number of innovative measurement, design and analysis features will be used to increase chances of discovering effective intervention possibilities. RELEVANCE: The problem of Army suicide is one of great importance because an effective military force requires its members to be not only physically healthy but also mentally healthy. The relevance of a current study of Army suicide is heightened by the alarming rise in the suicide rate of US Army personnel over the past five years. The research proposed here has the potential to be of great value in helping the Army select optimally effective interventions to address this problem.

Funding Organization: National Institutes of Health
Study Title: RNA editing in suicide, major depression and animal model of depression
Principal Investigator: Stella Dracheva
Year When Study First Received Funding: 2010
Abstract: DESCRIPTION (provided by applicant): The estimated global burden of suicide is about one million deaths per year. Being one of the leading causes of death, suicide receives increasing attention worldwide, with many countries (including USA) developing national strategies for prevention. Up to 90% of adults who commit suicide have at least one psychiatric diagnosis (e.g., major depressive disorder (MDD), bipolar disorder (BPD), schizophrenia (SZ)). Whether the biological underpinnings of suicide are distinct from those of the comorbid psychiatric disorders is unclear. In our "initial study" we examined mRNA editing of 5-HT2CR in the
prefrontal cortex (PFC) of persons who had suffered from BPD or SZ and died by suicide or other causes as well as in psychiatrically normal controls without suicides. We detected an increase in editing that was associated with suicide but not with the psychiatric diagnoses, demographic characteristics, psychoactive medications, alcohol or drug abuse. Based on these findings, we hypothesize that an alteration in the mRNA editing process may be one of the factors that predispose individuals toward suicidal behavior. The proposed application will investigate this phenomenon further to establish its specificity among different clinical populations and different brain regions as well as to elucidate molecular targets for future pharmacological interventions against suicidal behavior. Our initial study was focused on persons with BPD and SZ. However, given that the majority of suicides occur in persons with MDD, confidence in specificity of this phenomenon for suicidal behavior cannot be firmly established without studying 5-HT2CR editing in the context of MDD. In addition, our initial study was performed in the PFC that control decision-making and impulsivity. However, there is undoubtedly an affective component to suicide, which we will address in the proposed application by assessing editing in the amygdala and the anterior cingulate cortex. These two regions are the crucial elements of the corticolimbic circuitries that are involved in mood regulation and that are compromised in depression. In an attempt to tease out the anticipated 5-HT2CR editing changes in suicide from those that are induced by medications taken by the patients in the course of the disease, we will perform a parallel study using mice exposed to the unpredictable chronic mild stress (UCMS), which is an established model to study aspects of depression in animals. In particular, we will investigate editing alterations in UCMS-exposed mice with and without antidepressant treatment. The editing alterations (if observed) will be compared to those detected in humans with MDD and/or suicide. We will also take a first step toward elucidating the molecular mechanisms underlying the suicide-associated variations in editing. Although 5-HT2CR editing is influenced by many different factors, the most obvious explanation is an alteration in the activity of the editing enzymes (adenosine deaminases that act on RNA or ADARs). Thus, we will attempt to assess the activity of ADARs in suicide and/or MDD. PUBLIC HEALTH RELEVANCE: Despite dramatic improvements in the pharmacological treatment of psychiatric disorders associated with suicide, there has been relatively little change in suicide rates over the past 25 years. Effective pharmacological approaches toward suicidal behavior can be developed only if biological mechanisms specific for suicide are understood. According to our initial study, one of those suicide-specific mechanisms may initiate from an alteration in the mRNA editing process. The proposed application will investigate this phenomenon further, aiming to elucidate molecular targets for future pharmacological interventions against suicidal behavior.
expression of genes involved in neural and structural plasticity is significantly down-regulated in the
postmortem brain of suicide subjects, suggesting that altered gene expression may be crucial in the etiology of
suicide. Interestingly, a large number of genes exhibit an inverse correlation between the degree of
methylation and the magnitude of gene expression. Therefore, the possibility that epigenetic modifications of
DNA causing such alterations in the expression of certain genes in brain of suicide subjects, cannot be ruled
out. In fact, research in the area of epigenomic regulation of gene expression has led to the hypothesis that
the polygenic nature of complex psychiatric disorders might indicate that a common pathway is involved in
the dysregulation of multiple genes through an epigenomic mechanism. Although still in infancy, recent
evidence suggests that epigenetic factors may play a key role in the pathogenic mechanisms of psychiatric
illnesses. To investigate whether epigenetic modifications of DNA play any role in suicidal behavior, we are
proposing a pilot study to investigate large-scale epigenetic profiling in the prefrontal cortex of a cohort
comprising depressed suicide, non-suicide depressed and well-matched non-psychiatric healthy normal
comparison subjects. More specifically, we will examine the following: 1) DNA methylation pattern at the
promoters of all known protein-coding genes; 2) confirm microarray results using sodium bisulfite
modification-based mapping of metC/CAEC/T ratios in the CpG sites; 3) use a network-based approach to test
the modularity of the epigenomic data; and 4) combined analysis of epigenomic profiles and global gene
expression data. To further replicate the DNA methylation study, in another cohort of depressed suicide and
healthy comparison subjects, we propose to follow-up 10 to 15 promoters of genes that exhibit the largest
epigenomic differences between depressed suicide and normal control subjects. To our knowledge, the
proposed research will be the first of its kind in suicide research, and will likely identify major epigenetic
modifications in the suicide brain. The proposed studies will also pave the way for our future epigenetic
studies and will be crucial for identifying the etiological and pathogenic mechanisms of suicide.

PUBLIC HEALTH RELEVANCE: Our proposed study will yield important information on the neurobiology of suicide,
which may eventually lead to better treatment and possibly prevention of suicide.

Funding Organization: National Institutes of Health
Study Title: Lithium’s Molecular Mechanism of Action and the Pathology of Bipolar Disorders
Principal Investigator: Ramin Parsey
Year When Study First Received Funding: 2011
Abstract: DESCRIPTION (provided by applicant): Bipolar disorder (BPD) is a brain disorder characterized by
recurrent manic and major depressive episodes with a one year prevalence rate between 1-2%.1 BPD ranked
20th in terms of causes of loss of disability-adjusted life-years in 1992 and is associated with a life time
suicide risk of up to a 19%.3 The main burden of illness in BPD is in the depressive pole. A deficiency of
serotonin (5-HT) function has been postulated to underlie depressive episodes yet few studies have examined
indices of 5-HT neurotransmission in the brain in BPD. It is widely acknowledged that there are significant gaps
in the current identification and treatment of bipolar depression.5-8 Better understanding of the
neurotransmission deficits in BPD may aid diagnosis, identification of biomarkers and treatment targets to
facilitate treatment development and ultimately to assist in treatment selection. Our preliminary data with
[11C]DASB shows lower binding in BPD. We propose to determine the extent and nature of abnormalities of 5-
HTT binding in vivo using positron emission tomography (PET) in medication-free bipolar I depression. We
hypothesize that BPD has lower 5-HTT binding compared to controls. We will also investigate the 5-HT effects
of a common treatment for BPD, lithium. Discovered decades ago, lithium remains one of the few effective
treatments in BPD, with evidence of mood stabilizing, antidepressant, antisuicidal, and even neuroprotective
qualities and is considered to be first line treatment. The actions of lithium on 5-HT indices may be central to its antidepressive and antisuicidal properties. We hypothesize that lithium downregulates presynaptic 5-HT1A receptor binding, upregulates postsynaptic 5-HT1A binding, upregulates 5-HTT binding, and these molecular effects will be related to clinical improvement, both in depression and suicidality. 5-HT1A binding potential will be determined using [11C]WAY 100635. We propose to perform [11C]DASB and [11C]WAY 100635 scans in 38 medication free BPD I subjects during a major depressive episode and compare 5-HTT and 5-HT1A binding potential in 38 healthy volunteers. We will also examine the diagnostic specificity of lithium response by studying 10 unipolar depressed subjects in an identical manner. We will examine the pharmacological specificity of lithium by studying lamotrigine in BPD subjects. Finally, we will also assess the ability of baseline scanning to predict treatment response. All BPD subjects will be treated with lithium and have repeat scans with both radiotracers. Many with BPD do not tolerate lithium's side effect burden, and it has a narrow therapeutic window. In this grant period we will determine at which 5-HT protein(s) lithium exerts its antidepressant and antisuicidal properties. Ultimately this can lead to novel therapeutics that are better tolerated. We will independently advance our understanding of the molecular pathophysiology of BPD as well as characterize the mechanisms of action of lithium. PUBLIC HEALTH RELEVANCE: Bipolar disorder or manic depressive illness is a very common and devastating brain illness. Very little is known about the biological basis of this illness and less is known about the mechanism of action of our commonly prescribed medications. With this proposal we will significantly increase our understanding of both the illness and its treatment using state of the art brain imaging technologies.

Funding Organization: National Institutes of Health
Study Title: Attempted Suicide Candidate Gene Resequencing
Principal Investigator: Virginia Willour
Year When Study First Received Funding: 2011
Abstract: DESCRIPTION (provided by applicant): This application aims to identify novel gene variants conferring susceptibility to suicidal behavior. While suicidality is perhaps the most dreaded aspect of psychiatric disorders, and among the leading causes of death among young people in the United States, relatively little research has been devoted to its biological basis. Yet family, twin, and adoption studies make clear that suicidal behavior has a substantial heritable component. While there is evidence that this heritability is accounted for in part by a liability to mood disorder, other evidence suggests an independent heritable facet that may cut across multiple psychiatric disorders. This independent feature has been hypothesized to be a liability to aggressiveness and impulsivity; the genetic study of this feature has focused on serotonergic genes because of neurobiological findings in suicidal subjects implicating this neurotransmitter. However, little systematic genetic investigation of the suicidality phenotype has been undertaken. Only in the last six years have the first attempts been made to examine the whole genome for linkage with this phenotype. The first two published studies of this kind, one using alcoholism pedigrees and the other using major depression pedigrees, both found evidence of linkage to the 2p11-12 region. Remarkably, when we examined the suicidal behavior phenotype in our bipolar disorder pedigree set, we found that the strongest evidence for linkage across the genome was in the same region, at the same markers implicated previously. This impressive confluence of findings across three genome-wide studies using differing sample types strongly suggests the presence of a gene predisposing to suicidal behavior in the 2p11-12 region. We tested this hypothesis directly in a genome-wide association study by comparing genotypes from subjects with bipolar disorder and a history of attempted suicide (attempters) to those from subjects with bipolar disorder and no history of attempted
Suicide (non-attempters). This analysis identified the LRRTM4 gene, which encodes a nervous system transmembrane protein that triggers formation of excitatory synapses and localizes to 2p12. An independent case-control association study using the attempted suicide phenotype also identified the LRRTM4 gene. We propose to follow-up these results by conducting a large-scale resequencing effort designed to identify a catalog of risk alleles for LRRTM4, with the goal of identifying genetic variation that increases the risk of suicidal behavior, thereby providing unprecedented insight into the genetic basis of the phenotype. Our project will make use of the diverse and complementary skill sets of an outstanding team of investigators that includes experts in molecular genetics, statistical genetics, bioinformatics, and psychopathology. Finding genetic variants that influence suicidal behavior would allow for the identification of people with high-risk alleles and the identification of medications that influence suicidal behavior in individuals with these high-risk alleles. It would also provide new insights into the biological basis of suicidal behavior and provide new therapeutic targets. PUBLIC HEALTH RELEVANCE: Suicidal behavior is perhaps the most dreaded aspect of psychiatric disorders and among the leading causes of death for young people. This application aims to identify genetic factors that increase the risk for suicidal behavior.

**Funding Organization:** National Institutes of Health  
**Study Title:** Suicide Epigenetics  
**Principal Investigator:** Virginia Willour  
**Year When Study First Received Funding:** 2012  
**Abstract:** DESCRIPTION (provided by applicant): Suicidal behavior is a complex phenotype that includes both attempted and completed suicide. Family, twin, and adoption studies provide strong evidence for a heritable component to suicidal behavior. This heritability appears to be partly dependent on the presence of psychiatric disorders such as bipolar disorder, depression, and alcoholism. Importantly, the heritability also appears to be partly independent of them. Our ongoing studies on the genetics of suicidal behavior have identified linkage regions on 2p11-12 and 6q25-26 and one genome-wide association signal on 2p25 (p=5.07 X 10^-8), findings that may lead to important advances in understanding the biological basis underlying suicidal behavior. However, a fuller picture will only emerge as the interaction of genetic susceptibility variants with other factors, such as personality traits and environmental risk factors, are established. Environmental stressors, such as child abuse and early parental loss, are known to play important roles in triggering suicidal behavior, likely through interaction with genetic vulnerability factors. Recent work showing stress-mediated epigenetic control of BDNF, a gene implicated in suicidal behavior, provides molecular evidence that epigenetic mechanisms can mediate this interaction (Tsankova et al., 2006). These results suggest the possibility that new insights into the etiology and pathophysiology of suicidal behavior can be gleaned from further study of epigenetic modifications in post-mortem brains of suicide completers. The tools to perform large-scale epigenetic studies have only just become available, and our Epigenetics Center at Johns Hopkins has been a leader in the development of such tools, having created the Comprehensive High-throughput Arrays for Relative Methylation (CHARM) method for genome-wide DNA methylation (DNAm) studies (Irizarry et al., 2008). We are now proposing to conduct a genome-wide assessment of DNAm using CHARM and samples from the frontal cortex (BA10) of post-mortem brains taken from mood disorder suicide completers and controls. Promising DNAm regions will then be validated using bisulfite pyrosequencing, and validated candidate genes will be screened for differential expression in suicide completers. To accomplish this, we have assembled an outstanding team of investigators with expertise in epigenetics, genetics, biostatistics, and psychopathology. The identification and characterization of differentially methylated genes and genomic
regions in suicidal behavior would a) provide new insights into the biological basis of suicidal behavior; b) provide new therapeutic targets; and c) provide the data needed to generate in vivo models in which to test therapeutic targets. These new insights into suicide pathogenesis might allow for dramatic advances in our ability to reduce the global burden of this devastating phenotype. PUBLIC HEALTH RELEVANCE: Suicidal behavior is perhaps the most dreaded aspect of psychiatric disorders and among the leading causes of death for young people. This application aims to identify epigenetic modifications that increase the risk for suicidal behavior.

**Funding Organization:** National Institutes of Health  
**Study Title:** Integrative Analysis of Transcriptome, Genome and Disease Diversity in Major Depressive Disorder  
**Principal Investigator:** George Tseng  
**Year When Study First Received Funding:** 2012  
**Abstract:** DESCRIPTION (provided by applicant): Major depressive disorder (MDD) is a heterogeneous illness with many clinical variables - such as sex, age, alcohol, antidepressant drug, recurrence or death by suicide -- as potential factors characterizing subtypes of MDD, making it difficult to fully understand its underlying mechanisms and heterogeneous genetic underpinnings. Many transcriptomic studies have been generated in the literature, including those from Dr. Sibille, the co-PI on this proposal. We propose to apply state-of-the-art statistical integrative analyses tailored to combine multiple MDD transcriptomic studies that will address the specific issues of case-control pairing design, confounding clinical variables and small sample size. Our study will detect novel MDD associated biomarkers, pathways and co-expression modules, and elucidate the magnitudes of transcriptomic changes attributable to substance abuse, recurrence, disease severity, age and sex. The results will enhance our understanding to MDD genetic mechanisms and lead to better and individualized therapeutic solutions. PUBLIC HEALTH RELEVANCE: Our proposed research is to develop and apply modern genomic meta-analysis methods to combine multiple major depressive disorder (MDD) transcriptomic studies that will adequately model the specific data structure of case-control pairing design, confounding clinical variables and small sample size. The goal is to detect novel MDD associated biomarkers, pathways and co-expression modules, and elucidate the magnitudes of transcriptomic changes attributable to substance abuse, recurrence, disease severity, age and sex. The results will enhance our understanding of MDD genetic mechanisms and lead to better and individualized therapeutic solutions.

**Funding Organization:** National Institutes of Health  
**Study Title:** Genetic Risk Factor for Suicidal Behavior  
**Principal Investigator:** Virginia Willour  
**Year When Study First Received Funding:** 2012  
**Abstract:** DESCRIPTION (provided by applicant): This proposal aims to identify and characterize novel gene variants conferring susceptibility to suicidal behavior. We will do this both through intensive follow-up of a strongly implicated chromosomal region, and through performing the first ever exome-wide search for rare variants related to this phenotype. While suicidality is perhaps the most dreaded aspect of psychiatric disorders, relatively little research has been devoted to its biological basis. Yet family, twin, and adoption studies make clear that suicidal behavior has a substantial heritable component. While there is evidence that this heritability is accounted for in part by a liability to mood disorder, other evidence suggests an independent heritable facet that may cut across multiple psychiatric disorders. This independent feature has
being hypothesized to be a liability to aggressiveness and impulsivity, the genetic study of which has focused on serotonergic genes. However, little systematic genetic investigation of the suicidality phenotype has been undertaken. In the first iteration of this grant, we conducted an attempted suicide genome-wide association study (GWAS), which generated an association signal on 2p25 at rs300774 (p=5.07 X 10-8), a finding that is on the threshold of genome-wide significance (p<5X10-8). The associated SNPs on 2p25 fall in a large linkage disequilibrium block that contains the ACP1 gene, whose expression is significantly elevated in bipolar disorder (BP) subjects who have completed suicide. Furthermore, the ACP1 protein is a tyrosine phosphatase that interacts with beta-catenin. The connection to beta-catenin, a key molecule in the Wnt signaling pathway, is noteworthy because the Wnt pathway is positively regulated by lithium, which has been shown to decrease suicidal behavior. The connection between suicidal behavior and beta-catenin was further supported by our gene set enrichment analysis of our attempted suicide GWAS dataset and by our initial whole-exome sequencing of 39 BP attempters and 60 BP non-attempters. We propose to follow up these findings by resequencing the 2p25 candidate region and by conducting a secondary analysis of whole-exome data from 800 attempters and 1,200 non-attempters, allowing us to search for functional variants influencing the risk for suicidal behavior on 2p25, in Wnt-related genes, and throughout the genome. To accomplish this, we will employ the diverse and complementary skill sets of an outstanding team of investigators including experts in molecular genetics, statistical genetics, bioinformatics, neurobiology, and psychopathology. The identification of candidate genes and functional variants associated with suicidal behavior would have a significant public health impact because it would provide new insights into the biological basis of suicidal behavior, provide new therapeutic targets, and provide the data needed to generate in vivo models in which to test therapeutic targets. PUBLIC HEALTH RELEVANCE: Suicidal behavior is perhaps the most dreaded aspect of psychiatric disorders and among the leading causes of death for young people. This proposal aims to identify genetic factors that increase the risk for suicidal behavior.

Funding Organization: National Institutes of Health
Study Title: Toll-like Receptors and Cytokines in Depression and Suicide Brain
Principal Investigator: Ghanshyam Pandey
Year When Study First Received Funding: 2012
Abstract: DESCRIPTION (provided by applicant): Suicide is a major public health concern. About 30,000 people die each year by suicide in the USA alone, and about one million people die from it worldwide. Depression is a major risk factor for suicide. Several studies indicate that suicide is also associated with abnormal neurobiology, such as altered serotonin function and signaling mechanisms. Some studies also suggest abnormality of the immune function in depression and suicide. This is based on the observation of increased levels of proinflammatory cytokines, which are major mediators of immune function, in the serum and CSF of depressed and suicidal patients and the observation that administration of cytokines, such as TNF-α, to cancer patients induces symptoms similar to those of depression. Some recent studies indicate abnormalities of proinflammatory cytokines in the brain of depressed and suicide subjects. Cytokines and chemokine are important biological mediators of immune function. However, it appears that Toll-like receptors (TLR), which may be the first line of defense against pathogens and tissue damage, are also major mediators of innate immunity. Upon activation by specific ligands, TLRs induce downstream signals that lead to cytokine and chemokine production, which can initiate a localized inflammatory response. In order to examine the role of cytokines and TLRs in depression and suicide, we are proposing a comprehensive study of TLRs, cytokines and chemokines in postmortem brain of depressed and suicide subjects. The proposed studies are also based on
our preliminary findings from a gene profile study indicating alteration (up- or down-regulation) of 14 genes in depressed suicide victims. These altered genes include certain cytokines, chemokines and TLRs. The main objectives of our proposed studies are to examine in detail the specific TLR and cytokine genes that are altered in suicide and depressed brain, and if these altered genes are specific to suicide (independent of diagnosis) or these alterations are also shared by non-suicide depressed subjects. To achieve this objective we will conduct a gene profile study in the dorsolateral prefrontal cortex (DLPFC) and hippocampus of four groups of subjects which include: 1) normal controls, 2) depressed suicide, 3) non-depressed suicide, 4) non-suicide depressed subjects. We will then validate these findings by determining the mRNA and protein expression of altered genes, which we find to be about 14 in these subjects. These studies may be significant as they may result in identification of important bio- and vulnerability markers for depression and suicide and may provide useful targets, such as TLR-3, for developing newer therapeutic agents. This may be innovative as it may be the first comprehensive study of cytokines, chemokines and TLRs in depression and suicide and is significant for understanding the pathophysiology of depression and suicidal behavior and its treatment. PUBLIC HEALTH RELEVANCE: Suicide is a major public health problem and about 30,000 people die of suicide in the USA every year, and about one million people die from it worldwide. However, the neurobiology of suicide is unclear. Abnormalities of cytokines, which are considered hormones of the immune system, have been implicated in suicide. Besides cytokines, chemokines and Toll-like receptors (TLRs) are other mediators of immune functions. In order to examine if abnormalities of immune function are involved in the pathophysiology of suicide we are proposing a study of neuroimmune genes in the postmortem brain of normal controls, suicides victims and depressed subjects. These studies may identify vulnerability genes for suicide and newer targets for developing therapeutic agents for treatment of depression and prevention of suicidal behavior. These studies may also provide an understanding of the role of the immune function in depression and suicide.

**Funding Organization:** National Institutes of Health  
**Study Title:** Metallothioneins and Polyamines in Major Depression and Suicide  
**Principal Investigator:** Adolfo Sequeira  
**Year When Study First Received Funding:** 2012  
**Abstract:** DESCRIPTION (provided by applicant): Approximately 30,000 Americans die every year by suicide, more deaths than those caused by HIV and homicides combined. Major depressive disorder (MDD) patients have the highest rates of suicidal behaviors, however only a subset ever commit suicide, making the identification of a molecular signature for suicide a major clinical challenge in this high risk population group. We and others have observed specific gene expression alterations in two stress response molecular mechanisms, metallothioneins and polyamines, in brains of MDD suicide victims, with opposite effects however in MDD patients who died of other causes. These stress-related mechanisms have not been carefully studied at the genetic, epigenetic, RNA, and protein level in a sample of subjects allowing the comparison between suicide, non-suicide depressed cases, and normal controls in post-mortem brain tissue. The central hypothesis of this proposal is that metallothioneins, and polyamines, two key molecular stress-response mechanisms, are impaired in MDD subjects that commit suicide. This study proposes to investigate, at the molecular level, the role played by polyamines, and metallothioneins in suicide in MDD patients. (Aim 1) We hypothesize specific gene and protein expression alterations in suicide and non-suicide MDDs compared with control subjects. Twenty MDD suicides, 20 non-suicide MDDs and 20 controls matched in terms of age and gender will be analyzed for a total of 60 subjects. We will investigate six brain regions relevant to suicide, and mood disorders, including the anterior cingulate cortex (ACC), amygdala (AMY), dorsolateral prefrontal cortex...
(DLPFC), hippocampus (HIPP), nucleus accumbens (NAcc), and orbitofrontal cortex (OFC) which form circuits that regulate emotional stimuli processing and change in mood states. (Aim 2) We hypothesize that stable gene and protein expression differences in suicide will be associated with genetic and epigenetic variation for the genes selected from Aim 1 using the same cohort of subjects from Aim 1. (Aim 3.1) We hypothesize that relevant biomarkers will be found in subjects for which we have both blood and brain tissue. We will attempt to validate the identified molecular targets in a new cohort of subjects (20 MDD suicides, 20 MDD non-suicides, 20 controls) (Aim 3.2) We hypothesize that medications and cortisol will have differential effects on serious MDD suicide attempters compared to MDD non-attempters, and normal controls. We will determine the effects of cortisol and antidepressants on polyamine, and metallothionein gene and protein expression. These immortalized cell lines, derived from patients with severe suicide attempts, patients without suicide attempts or thoughts, and matched controls (25 cell lines per group, 75 in total). Taken together, this project involves a large number of high quality brain samples, blood samples and a mechanistic cellular confirmation component to identify potential biomarkers in molecular stress response systems. These biomarkers might play a significant role in the identification of MDD patients with high risk of committing suicide and might offer promising targets for pharmacological interventions. PUBLIC HEALTH RELEVANCE: Project Narrative 30,000 deaths each year in the US are due to suicide mainly among people suffering from psychiatric disorder and particularly from major depressive disorder. Current diagnostic algorithms are inadequate and the identification of individuals at high risk for suicide is frequently overlooked. The focus of this proposal is to study the role of three molecular response mechanisms to stress (polyamines and metallothioneins) in suicide predisposition for patients with major depressive disorder.

**Funding Organization:** National Institutes of Health  
**Study Title:** Animal Models of Suicide Relevant Intermediate Behavioral, Neurobiological and M  
**Principal Investigator:** Frances Champagne  
**Year When Study First Received Funding:** 2013  
**Abstract:** The experience of childhood adversity in the form of neglect/abuse is a major risk factor for future suicidal behavior perhaps via long-term changes in molecular and neurobiological substrates of anxiety, depression, and impulsivity/aggression. The mechanistic links between childhood adversity, molecular/neurobiological pathways, and suicide risk have yet to be established. We propose to investigate key hypotheses regarding: 1) whether childhood adversity is a causal antecedent to suicide behavioral, neurobiological, and molecular phenotypes; 2) the time course of adversity-induced effects on gene expression and epigenetic variation within target gene clusters: 3) the degree of concordance between peripheral cell epigenetic marks and those present in the brain; and 4) explore reversal of such effects by "therapeutic" intervention. We propose to use mouse models as mice are especially well suited to mechanistic studies. Our experiments are designed to parallel the molecular and neurobiological human studies within the center and can thus readily inform the other projects. In Aim 1, we will investigate whether suicide-relevant phenotypes in mice induced with early life adversity are associated with indices of HPA dysregulation, neurobiological changes, and gene expression patterns in the brain. Heightened stress responsivity is risk factor for the emergence of psychopathology and this aim will establish the HPA function of maternally separated mice that exhibit risk phenotypes (anxiety-like, depressive-like, impulsivity/aggression). This aim will also determine the density of 5-HTT and 5-HT1AR binding in the brain as a function of maternal separation/risk phenotype and assess the expression of genes within serotonergic, HPA, and neurotrophic pathways, as these are biological phenotypes linked to suicide. In Aim 2, we will determine the role of
epigenetic variation in the form of DNA methylation as a potential molecular pathway of maternal separation-induced effects. Aim 2 determines whether separation-induced epigenetic effects in the brain correspond to changes in blood and whether these peripheral epigenetic changes can be used to predict the later development of a suicide-relevant risk phenotype. In Aim 3 we will explore the reversibility of maternal-separation-induced effects on suicide-relevant phenotypes using pharmacological targeting and environmental manipulations during the juvenile period.

**Funding Organization:** National Institutes of Health  
**Study Title:** Biomarkers in HPA Axis and Inflammatory Pathways for Suicidal Behavior in Youth  
**Principal Investigator:** Nadine Melhem  
**Year When Study First Received Funding:** 2013  
**Abstract:** DESCRIPTION (provided by applicant): There is a pressing need to detect biological signatures, or biomarkers, for psychiatric diseases that will improve our understanding of their architecture of risk and methods of diagnosis and treatment, as their public health burden continues to grow alarmingly. This is especially true for suicide and suicidal behavior, the most serious sequelae of psychiatric diseases and the 3rd leading cause of death among adolescents and young adults. While suicidal behavior occurs in the context of psychiatric disorders, relatively few subjects with psychiatric disorders attempt suicide. Hypothalamic-pituitary-adrenal (HPA) axis dysregulation is postulated as one of the pathways between stress, psychiatric diseases, and suicidal behavior. In this R21 pilot study, we propose to examine hair cortisol concentrations (HCC) in psychiatric inpatients, 13-25 years of age, admitted for suicide attempt (n=35) and compare them to psychiatric inpatients with suicidal ideation but no previous history of attempts (n=35) and healthy controls (n=35). HCC is a marker of chronic activation of the HPA axis as it provides a retrospective assessment of cortisol levels over the past few months and thus will provide an assessment of cortisol levels prior to suicide attempt. This temporal assessment is not possible using standard methods of HPA axis measurement. This R21 study is the first to use this innovative method in the context of suicidal behavior. HPA axis dysregulation also affects the inflammatory response. We propose a model for the biological pathways to suicidal behavior where we will examine the pathways from gene expression in the HPA axis and inflammatory pathways in peripheral blood to HCC, glucocorticoid receptor (GR) sensitivity, systemic levels of inflammation (Interleukin-6, C-reactive protein), clinical correlates of suicidal behavior, and suicidal behavior. This study is also the first to examine peripheral gene expression and the relationship between the HPA axis and inflammatory pathways in relation to suicidal behavior. We hypothesize that suicide attempters will have decreased GR expression, increased HCC, decreased GR sensitivity, increased expression of inflammatory genes, and increased inflammation as compared to the other two groups. These biological measures will be associated with increased sleep disturbances, impulsive aggression, emotion dysregulation, and reduced distress tolerance. Biological and clinical measures will together predict suicidal behavior. This study is in line with NIMH's Research Domain Criteria (RDoC) where we are measuring the sustained threat construct of the negative valence systems in subjects who are on the spectrum of suicidal behavior from normal to ideation and attempt. This R21 study is the first exploratory stage of a future project that will examine the clinical efficacy of HCC and test our proposed model for the biological pathways of suicidal behavior in larger samples. Achieving these goals will bring innovative methods to clinical practice to detect individuals at high risk and will result in the development of new treatment approaches, which will both lead to a significant reduction in psychiatric morbidity and mortality resulting from suicidal behavior in youth.
U.S. National Suicide Prevention Research Efforts: 2008-2013 Portfolio Analyses
Short-Term Research Objective 1.B.

**Funding Organization:** National Institutes of Health

**Study Title:** Genetic Analysis of High-risk Utah Suicide Pedigrees

**Principal Investigator:** Hilary Coon

**Year When Study First Received Funding:** 2013

**Abstract:** DESCRIPTION (provided by applicant): Suicide is a significant health concern. There are over 33,000 suicide deaths per year in the United States, accounting for 1.3% of all fatalities (WISQARS, 2005), and about 2% of deaths worldwide (World Health Organization, 2000). Aggregated data across multiple large studies has produced heritability estimates of completed suicide of 45%. The Rocky Mountain States have much higher age-adjusted suicide rates, and Utah is consistently in the top ten. In Utah, suicide is the leading cause of death for males between the ages of 15 and 54. Our project will use a large DNA resource already collected from decedents through a long-term collaboration with the centralized Utah State Office of the Medical Examiner (OME). Records of >2,000 decedents with DNA were linked to the Utah Population Databank (UPDB), a computerized genealogy database that includes medical data, demographic information, and genealogical data for over 6.5 million individuals. Using the UPDB, we identified 27 high risk families containing ~150 suicide decedents with DNA. As a rare condition (1-2/10,000 per year), aggregation of suicide completion in high-risk pedigrees represents a unique resource to study risk factors. We will use the genealogical, demographic, and medical data in the UPDB to identify and focus on the most compelling of these high-risk suicide pedigrees; those that contain both a significant excess of suicide completion and that exhibit the most discriminating characteristics compared to non-familial suicide. By using these phenotypic comparisons to choose the most unique high-risk pedigrees, we will increase homogeneity and strengthen our ability to isolate genetic variants related to suicide risk. These discriminating phenotypes will also identify non-genetic factors associated with high familial risk that can foster other epidemiological studies, and can facilitate future gene x environment analyses. We currently have in hand a large resource of DNA and phenotype information from ~2500 additional Utah suicide decedents. This sample will grow to over 4000 DNAs by the end of the study, the largest population-based sample of DNA from suicide decedents ever collected. We propose to focus on unusual high-risk suicide pedigrees with increased likelihood for more penetrant rare genetic variation, followed by confirmation and follow-up analyses in large cohorts of Utah decedents and publicly-available psychiatric data sets. The detection of genetic variants associated with suicide could shed light on biological pathways leading to suicide risk in the population, or in association with specific disorders. We have chosen state-of-the-art analytical methods, and have assembled a team of experts (analytic, phenotypic, and molecular) to explore these unique data resources to identify genetic risk factors for suicide. The detection of rare variants associated with suicide could shed light on biological pathways leading to suicide risk in the population, or in association with specific disorders.

**Funding Organization:** National Institutes of Health

**Study Title:** Clinical Evaluation Core

**Principal Investigator:** Maria Oquendo

**Year When Study First Received Funding:** 2013

**Abstract:** The Clinical Evaluation Core’s (CEC) goals are: 1. Recruitment, Characterization and Retention of Human Subjects 2. Uniform Diagnostic Method and Clinical Assessment Battery Across All Projects Including Psychological Autopsies, 3. Methods Development. 4. Maintenance of Reliability among Clinical Staff. 5. Supervise Inpatient Study Phase and Conduct Outpatient Study Phase 6. Consultation to Investigators. The CEC
identifies and recruits patients with MDE and post-mortem cases. Normal volunteers are recruited to provide normative values on measures used and to establish psychometric properties of measures in a nonpathological population. The CEC utilizes a core of clinical instruments covering major risk factor domains for suicidal behavior, and ensures uniformity of assessment domains and measures across the projects of the Conte Center. These assessments include Axis I and II diagnostic interviews, measures of state and trait-related risk factors, measures of suicidal behavior, demographic history, life events, social functioning, family psychiatric history. Assessments are performed at intake, at time of biological procedures, at discharge. CEC interacts extensively with other Cores and Projects in the Conte Center. The CEC conducts clinical evaluation, data collection and treatment for all Conte Center projects that include human subjects including the Clinical Project 5, PET Project 3, MRI Project 4 and Statistics Project 6. CEC works closely with the Data Management and Statistics Core (DMSC) staff to generate forms, data management procedures, and reliability statistics. CEC coordinates with the Brain Imaging Core (BIC) regarding subject recruitment, clinical interviewing, matching controls and monitoring drug washouts and subject flow through the brain imaging protocols. The CEC conducts assessments of the suicide victims whose brains are studied by the Postmortem Brain Studies Core (PMC). The CEC obtains blood, hair and saliva from subjects to be analyzed by the Neurobiology Laboratory Core (NLC). The CEC also interfaces with the Administrative Core to identify and recruit new staff and maintain a central database of CEC manuscripts. The CEC coordinates the diagnostic consensus conference for projects # 1, 2 - 6 and maintains inter-rater reliability. CEC Faculty and staff are an experienced center structure as most have worked as a core for the past 10 years or longer.

**Funding Organization:** National Institutes of Health  
**Study Title:** Neurobiology of Suicide: Childhood Adversity and Epigenetics  
**Principal Investigator:** Victoria Arango  
**Year When Study First Received Funding:** 2013  
**Abstract:** Childhood adversity is associated with greater risk for adulthood depression (MDD), aggressive traits and suicide. The biological basis of this relationship is mostly unknown but for the interesting finding of DNA methylation/less expression of the glucocorticoid receptor (GR) gene in suicides reporting childhood adversity. Stress and suicide are also associated with fewer cells and dendritic shrinkage in prefrontal cortex (PFC) and hippocampus (HC). Smaller HC volume may constitute a risk factor for stress-related psychopathology. In MDD suicides we find lower serotonin transporter (5-HTT) and higher serotonin IA receptor (5-HTIA) binding in PFC and higher rate of childhood adverse events. We hypothesize that this neurobiological phenotype may result from genes, environment and epigenetic effects. We aim to determine whether 5-HT1A binding, BDNF, measures of the hypothalamus-pituitary-adrenocortical (HPA) axis and candidate gene expression and methylation levels, correlate with neuron and glia density or number in PFC and HC in 5 groups of age- and sex-matched MDD suicides and nonpsychiatric controls with and without reported childhood adversity (before 15y) and 12 non suicide MDDs, all with psychological autopsy and brain toxicology. We propose to measure: 1) neuronal and glial density in dorsal PFC (dPFC) and ACC and estimate total number in HC; 2) 5-HTT and 5-HTIA binding in dPFC and ACC and number of 5-HT1A-immunoreactive (IR) Axonal Initial Segments in the granule cell layer of the dentate gyrus (DG) of the HC and BDNF-IR neuron density or number in dPFC and ACC and BDNF-IR cell number in HC; 3) Determine the effect of childhood adversity on HPA axis indices in dPFC, ACC and HC, and regional correlations with neuron number or density; 4) Determine the effect of childhood adversity on neuronal gene expression and methylation levels of 18 candidate genes in dPFC, ACC and HC in the same 5 groups as Aim 1. Exploratory aims will: 1) separate the effect of MDD from that of suicide or
adversity on neuron, glia and BDNF-IR cell density, in dPFC and ACC, or number, in HC, comparing the suicide and non-suicide MDD groups; 2) test the relationship between lifetime aggression scores and childhood adversity, neuron and glia number or density, serotonin indices, HPA axis indices, gene expression and methylation.

**Funding Organization:** National Institutes of Health  
**Study Title:** Neurotransmitter Imaging in Vivo in Mood Disorders and Suicidal Behavior  
**Principal Investigator:** Joseph Mann  
**Year When Study First Received Funding:** 2013  
**Abstract:** Project 3 takes postmortem neurotransmitter findings in suicides with MDD and radioligand development of the last five years and brings them together in a fashion that is best done with in vivo positron emission tomography (PET). We and others find abnormalities of the serotonergic system, principally the serotonin IA receptor (5-HTIA) and serotonin transporter (5-HTT) postmortem in depressed suicides. We have pilot PET data indicating that low 5-HTT binding in the same brain regions as suicides in MDD suicide attempters compared with MDD nonattempters and healthy volunteers. This indicates a potential suicide-related biological endophenotype in suicides that may be detectable in MDD before the first suicide attempt. In this project we seek to determine whether this is an endophenotype that is present before the first suicide attempt or onset of MDD, and its relationship to childhood adversity. We have found that 5-HTT binding is lower in depressed patients with reported childhood adversity. Rodent studies indicate that early adversity alters 5-HTIA binding. Specifically, we hypothesize that [11C]DASB 5-HTT binding will be low in MDD attempters and childhood adversity will contribute to this effect. With our new agonist 5-HTIA radiotracer, [11C]CUMI-101, we predict higher 5-HTIA agonist binding in MDD attempters as seen in suicides. We hypothesize that the 5-HTIA and 5-HTT binding in MDD suicide attempters, compared with MDD nonattempters and controls, will parallel findings in suicides. Both PET tracers will be used in the same groups to determine which tracer is best to detect differences between the groups, and these data will be used by Dr. Ogden in P6. To determine if this is a potential endophenotype, we will scan a group of high-risk offspring of MDD attempters before their first suicide attempt or episode of MDD. In the last two years of the project we will study new neurotransmitter targets to expand our knowledge base about suicidal behavior. We will determine monoamine oxidase A (MAOA) levels in healthy volunteers and MDD suicide attempters. MAOA is upregulated in MDD and responsible for the degradation of synaptic serotonin, DA and NE. In the same patients/controls as for MAOA, we will evaluate the endogenous opioid neurotransmitter system, by quantifying the kappa opioid receptor. In collaboration with other Cores and Projects, we will examine the relationship between the binding measures, fMRI responses during appraisal, stress responses, aggressive traits and the effects of reported childhood adversity.

**Funding Organization:** National Institutes of Health  
**Study Title:** Perturbed Cell Signaling Network and Suicide Neurobiology  
**Principal Investigator:** Yogesh Dwivedi  
**Year When Study First Received Funding:** 2013  
**Abstract:** DESCRIPTION (provided by applicant): Suicide is a major public health concern. Suicidal behavior occurs in the context of a diathesis that is characterized by traits in multiple domains: behavioral, clinical, personality, and biologic. While the complexity of suicidal behavior requires a multi-faceted prevention
approach, the identification of neurobiological dysfunction is critical for the pharmacological interventions that may have protective effects against suicidal behavior. In this context, we have shown reduced BDNF gene expression and less activation of its cognate receptor TrkB in the brain of suicide subjects. In addition, we have found that p75NTR, a low affinity BDNF receptor is upregulated in the brain of these subjects. BDNF, which plays a critical role in neural plasticity and cell survival, essentially mediates its action via TrkB-mediated activation of extracellular signal-regulated kinase (ERK)1/2 and phosphoinositide 3 kinase (PI3K) signaling pathways. Abnormalities in these two signaling systems at the upstream levels were also found in the same brain areas of suicide subjects in which abnormalities were noted in BDNF/TRKB/p75NTR. These changes were present in all suicide subjects regardless of psychiatric diagnosis. To better understand the functional significance of altered BDNF signaling at molecular and cellular levels and their implications in the neurobiology of suicide, we propose to test the hypothesis that hypoactive BDNF/TrkB-mediated ERK1/2 and PI3K/Akt and overexpressed p75NTR will lead to modifications in the interaction and activation of downstream scaffolding/regulatory proteins, translational machinery, chromatin remodeling, and structural plasticity in the suicide brain. To test our hypothesis, in brain areas implicated in suicidal behavior, i.e., dlPFC and hippocampus (cerebellum as negative control brain region) from well-characterized and well-matched depressed suicide and non-psychiatric control subjects (n = 30 in each group), we aim to examine whether: 1) hypoactive ERK1/2 will lead to altered activation of substrates p90 ribosomal S6 kinase (RSK) and mitogen-and stress-activated kinase (MSK) and their mediated transactivation of transcription factors and chromatin remodeling; 2) hypoactive ERK1/2 and PI3K will lead to less active translational machinery, translation of postsynaptic genes, and altered dendritic morphology; and 3) altered PI3K/Akt and p75NTR will be associated with altered interactions of scaffolding proteins leading to c-Jun kinase (JNK) activation and altered expression and functional characteristics of downstream apoptotic regulatory proteins and neuronal apoptosis. To make sure that the effects are suicide specific, we will perform these studies in the same brain areas of an additional group of well-matched subjects who were depressed (no previous suicide attempt and no family history of suicide) and died by causes other than suicide (n = 30). Our proposed study will precisely and mechanistically assess the complexity of cellular signaling at the molecular, cellular, and functional levels in suicide brain and will have a significant impact in understanding not only the neurobiological basis of suicide but in designing more efficacious treatment strategies.

**Funding Organization:** Veterans Affairs  
**Study Title:** Serotonin 2C Receptor mRNA Editing in Suicide  
**Principal Investigator:** Stella Plevan (Dracheva)  
**Year When Study First Received Funding:** 2008  
**Abstract:** Suicide is the eleventh leading cause of death in the U.S., accounting for 32,439 deaths in 2004. Up to 90% of adults who commit suicide have at least one DSM-IV psychiatric diagnosis. A question that has remained unanswered is whether the molecular factors predisposing to suicide are distinct from those of the psychiatric disorders in which it occurs. Our study during the current funding period (01/05 - 12/07) provides evidence that they are. In this initial suicide study we examined the mRNA variants of one of the serotonin receptors --2C (5-HT2CR)--previously implicated in depression and suicide. We compared postmortem specimens from the prefrontal cortex (PFC) of patients who had suffered from one of two psychiatric conditions (Bipolar Disorder (BPD) or Schizophrenia (SZ)) prior to death and subsequently committed suicide, to those subjects who died of other causes (this second group included psychiatric patients (BPD or SZ) and normal controls). We detected variations in the mRNA editing of the 5-HT2CR that were associated with...
suicide but not with the comorbid psychiatric illnesses, demographic characteristics, alcohol or drug abuse. These variations predict a significant increase in the VSV isoform of the receptor that has decreased activity and potency compared to the non-edited receptor. Over-representation of the VSV isoform in the PFC may, therefore, represent a vulnerability factor that predisposes some individuals to suicidal behavior irrespective of BPD or SZ. We now propose several lines of investigation that will broaden our understanding of these initial findings. Our first aim is to elucidate the molecular mechanisms underlying the increased 5-HT2CR editing in suicide. We will accomplish this by examining a number of candidate targets that are involved in the process of editing in order to determine whether their function is altered in the PFC of suicide victims. These studies aim to identify some of the factors responsible for the observed differences in 5-HT2CR editing and will allow us to determine whether suicide-associated changes are restricted to the 5-HT2CR or are present in other editing targets. In our initial study we found that 5-HT2CR editing varied with history of suicide rather than with SZ or BPD; however, tissue specimens from suicides with MDD were not available for us to study. Because, more than 30% of all suicides occur in MDD patients, it is crucial to examine 5-HT2CR editing in this population. Our second aim is to investigate whether suicide in the context of MDD is associated with variations in editing similar to those that we have detected in SZ and BPD suicide victims. If so, the evidence will be strengthened that increased 5-HT2CR editing constitutes a true and specific suicide-associated factor.

Funding Organization: Veterans Affairs
Study Title: Neurobiology of Suicide Risk in Traumatic Brain Injury and Substance Abuse
Principal Investigator: Deborah Yurgelun-Todd
Year When Study First Received Funding: 2009
Abstract: Efforts at understanding the neurobiological correlates of traumatic brain injury (TBI), prefrontal function and suicidal ideation have thus far provided inconclusive results. Primary blast-related TBI is common in returning veterans and appears to produce neurophysiological changes that resemble diffuse axonal injury (DAI). Disruptions in brain neural circuits that support cognitive processing in individuals with TBI may result in deficits in executive function including reduced problem solving and decision-making capacity. Moreover, veterans with TBI are often co-morbid for substance abuse and it has been shown that use of alcohol and illicit drugs can further compromise executive mediated functions known to depend on the frontal cortex. It has been proposed that these functional deficits may lead to cognitive rigidity and psychological distress and thus may serve as markers for suicidal risk. The proposed research builds on existing neurobiologic models of frontal function and will extend our understanding of TBI related brain changes by applying functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) techniques. Accordingly, we will examine blood oxygen level dependent (BOLD) signal changes within the cingulate and dorsolateral prefrontal cortices as well as the amygdala in TBI subjects, with and without a history of substance abuse, to characterize the nature of these patterns of signal change (higher/lower) in relation to healthy control subjects. We will determine whether measures of white matter microstructure, as measured by DTI methods, are abnormal in TBI subjects, with and without a history of substance abuse compared with healthy control subjects. We will also examine the relationship between BOLD signal changes and reduced FA values and suicidal ideation. Lastly, we will test the hypothesis that reduced FA and reduced activation in frontal regions in both substance abusing and non- substance abusing TBI veteran groups is significantly correlated with suicidal ideation, and that the correlation will be stronger for the TBI plus substance abuse cohort. We believe the proposed studies will impact veteran’s health by providing important insights into the neurobiological correlates of suicide and TBI that may lead to new approaches for identification and treatment of behavioral consequences of TBI.
U.S. National Suicide Prevention Research Efforts: 2008-2013 Portfolio Analyses
Short-Term Research Objective 1.B.

PUBLIC HEALTH RELEVANCE: Traumatic brain injury (TBI) is an important medical problem for active combat veterans. The return of veterans from Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF), many of whom have suffered mild TBI, has emphasized the crucial importance of understanding the neurobiologic and neuropsychological consequences of this type of brain injury. Furthermore, several studies point to the urgent need to define the neurobiological and cognitive underpinnings of suicidal ideation and behavior in veterans with TBI with and without comorbid substance abuse/dependence disorders. The evaluation of the neurophysiologic and cognitive predictors of suicide risk and recovery are needed to improve treatments. We believe the proposed studies will impact veteran's health by providing important insights into the neurobiological correlates of suicide that may lead to new approaches for identification and treatment of behavioral consequences of TBI.

Funding Organization: Veterans Affairs
Study Title: Brain Chemistry and Altitude in Bipolar Disorder
Principal Investigator: Perry Renshaw
Year When Study First Received Funding: 2013

Abstract: Bipolar disorder is a prevalent and severe psychiatric disorder marked by alternating episodes of depression and mania. In the Department of Veterans Affairs (VA), nearly 80,000 Veterans received care for bipolar disorder in 2004, a 40% increase from 1999. Bipolar disorder imposes a substantial medical burden on Veterans, and is associated with the highest health care costs of any psychiatric disorder in the VA system. Moreover, in male Veterans bipolar disorder is a significant risk factor for suicide. The World Health Organization ranks bipolar disorder as the sixth leading cause of global medical disability. Despite decades of research, the illness remains poorly understood, and no new treatment has surpassed lithium's effectiveness for the majority of patients. There is a critical need for research studies aimed at understanding the neurobiology of bipolar disorder, to improve our diagnostic and treatment strategies. Brain pH is closely linked to affective functioning, and is influenced by a range of internal and external factors. One such environmental factor may be altitude. Extreme altitudes are associated with a decreased partial pressure of inspired oxygen, and this hypobaric hypoxia results in significant cognitive impairment. However, the effect of moderate changes in altitude on brain chemistry is not well understood. Recent publications show that within the U.S., altitude is associated with an increased rate of suicide that begins at the modest altitude of ~2,000 feet, an effect that may be strongest in bipolar disorder. In terms of endogenous factors, it is hypothesized that decreased brain pH in bipolar disorder may represent a biologic trait of the illness. Decreased brain pH has been linked to altered brain lactate and glutamate levels in bipolar disorder. Research is needed to clarify the relationship between mood, brain chemistry and altitude in bipolar disorder. To address this need, we propose to use magnetic resonance spectroscopy (MRS) neuroimaging together with clinical assessments, to study the relationship between brain pH, glutamate, lactate and altitude in Veterans with bipolar disorder. The proposal features a novel cross-sectional study design, in which brain scans will be performed on subjects with bipolar disorder at two altitudes: Salt Lake City, UT (4,700 feet) and Belmont, MA (44 feet). A total of 120 subjects will be enrolled, including 40 depressed bipolar subjects (20 per site), 40 euthymic bipolar subjects (20 per site), and 40 healthy controls (20 per site). All subjects will undergo MRS brain scans to measure their brain pH, glutamate and lactate levels. The proposed study will provide insight into the interrelationship of brain chemistry, mood state and altitude in bipolar disorder. The results of the study may help scientists develop new diagnostic methods, or new treatment approaches for Veterans with bipolar disorder.