

Molecular Imaging & Neuropathology Division (MIND)

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Overview

The Molecular Imaging & Neuropathology Division spans the research spectrum from basic cell biology to in vivo imaging, molecular genetics and treatment trials. It emphasizes translational research and employs a multidisciplinary approach to psychiatric research to examine the biological substrate of mental illness at multiple levels. The Division comprises laboratories and research groups that cover a wide range of subjects, including basic molecular signal transduction as well as laboratory animal and cellular model studies to treatment studies. More specific research areas include neuroanatomical mapping, quantitative morphometric and gene expression studies and postmortem brain studies of psychiatric disorders. In addition to carrying out research, the Division provides neuropathology services to the New York State Office of Mental Health (OMH).

The Division maintains an archival collection (brain bank) of specimens critical to carrying out research that, for example, helps to elucidate the triggers for suicide in some depressed individuals. The Brain Imaging group conducts functional and structural brain imaging studies in animals and human subjects. This subdivision develops novel PET ligands for monoamine receptors, enzymes and transporters, amyloid protein and peptide receptors. It studies disease processes, effects of gene variants and childhood adversity on brain biology, biologic predictors of treatment outcome and the use of biomarkers for studies of drug effect and the relationship of drug actions to occupancy of the hypothesized site of action.

The Molecular Imaging & Neuropathology Division (formerly Neuroscience) is one of the largest at NYSPI and conducts a range of basic and clinical studies. It has three center grants. The NIMH-funded Silvio O. Conte Center for the Neuroscience of Mental Disorders: The Neurobiology of Suicidal Behavior (PI: John Mann) investigates risk factors for suicidal behavior in mood disorders, schizophrenia, and personality disorders. The Conte Center utilizes human postmortem studies and translational approaches such as novel PET tracers for brain imaging, new peptide assays in cerebrospinal fluid, and an investigation of candidate genes and basic biologic and cognitive endophenotypes. The second center is the Moody Center for the Study of Early Onset Bipolar Disorder, headed by Maria Oquendo. This center seeks to use functional MR and genetics to detect early onset bipolar disorder as a step towards preventative intervention. The third center is the NIMH funded Developing Center Suicide Intervention Center headed by Barbara Stanley.

Staff

Brain Imaging

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Laboratory of Molecular Neuroanatomy &

The Diane Goldberg Laboratory for Molecular Imaging of Neural Disorders

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Administration

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Current Research

The major areas of clinical investigation have been the biological basis of mood, anxiety and psychotic disorders and borderline personality; the action of antidepressants and other psychotropics and; risk factors for suicidal behavior. Basic studies have involved studies of neurotransmitter systems and the action of antipsychotics and antidepressants.

Mood Disorders & Suicide Risk Clinical Research: Research in this area is wide-ranging and collaborative, building on the expertise of researchers both within the department of psychiatry and outside its borders. For example, the Moody Center, headed by Dr. Oquendo, has collaborators at the University of Pittsburgh and together they are increasing the field's understanding of self-injurious acts. Working in collaboration with Drs. Joe Terwilliger, Victoria Haghighi and Jim Russo of the Columbia Genome Center; René Hen of the Center for Neurobiology and Behavior; and Dr. David Brent of the University of Pittsburgh, the group is examining genetic and epigenetic influences on the manifestation of suicidal and self-harming behaviors. Several key genes have been found to be associated with mood disorders, substance abuse, aggressive/impulsive traits and suicidal behavior. A study of the familial transmission of depression, suicidal acts and impulsive-aggressive traits is funded by NIMH grants to Dr. Mann and Dr. Brent (in Pittsburgh). The Center also conducts studies of bipolar probands and their offspring.

Other studies underway include those of suicidal behavior in schizophrenia, pharmacological treatment for bipolar disorder and depression, as well as abnormal chemical activity in the brain:

- Drs. Michael Grunebaum, Gregory Sullivan, Leo Sher and Elizabeth Sublette conduct psychobiological studies of mood and psychotic disorders. Dr. Peter

Freed studies mood regulation and grief process using fMR while Drs. Ainsley Burke and Jill Harkavy Friedman train and supervise the clinical evaluation core research staff and work on aspects of familial transmission of adversity. The studies of suicidal behavior in schizophrenia are directed by Dr. Friedman. Neuropsychological studies of cognitive function and impulsiveness in mood, psychotic and personality disorders are conducted by Dr. John Keilp.

- Dr. Barbara Stanley conducts neurochemical and psychological investigations in borderline personality disorder. One of her NIMH grants supports a parallel group, randomized, double blind study of the efficacy of a psychotherapy called “Dialectical behavior therapy versus an SSRI medication in the prevention of suicidal behavior in borderline personality disorder.”
- Dr. Grunebaum has an NIMH grant to conduct a double blind, randomized treatment study comparing paroxetine and bupropion in the treatment of suicidal depressed individuals and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) provides funding for Drs. Stanley and Oquendo’s Developing Center for Interventions to prevent suicide.
- Drs. John Mann, Oquendo and Ramin Parsey have developed methods using PET for quantifying binding to serotonin receptors. These methods allow: study of mood disorders as well as research in the effect of treatment with medication or ECT, identification of high-risk patients, prediction of clinical response to antidepressants and the localization of regional brain abnormalities in high-risk patients. Studies by this team have helped to identify specific prefrontal cortical regions that determine lethality of suicidal behavior by mediating the degree of intent and impulsivity, which, in turn, determine the medical lethality of suicidal behavior. They have also mapped the brain regions with abnormal serotonin system function in depressed patients and identified regions of abnormality associated with specific components of psychopathology that predict short-term antidepressant response.

Personality Disorders: The main focus of research is the understanding of suicidal behavior, non-suicidal self injury and borderline personality disorder (BPD) from clinical, neurobiological, cognitive neuroscience and social perspectives. In addition, this group studies psychosocial and pharmacological interventions targeting suicidal behavior and non-suicidal self-injury across the diagnostic spectrum. Research projects also include the genetics of borderline personality disorder, the relationship of childhood trauma to suicidal and self-harm behaviors, fMRI studies of emotion regulation and rejection sensitivity in borderline personality disorder, the relationship of interpersonal factors, rejection sensitivity to suicidal and self-harm behaviors, and traits that might be amenable to treatment such as emotion dysregulation and impulsivity that may mediate genetic and/or environmental risk factors for the development of borderline personality, and that possibly mediate propensity for suicidal and self-harm. Other studies target social factors associated with the risk of developing BPD and related self-harm behaviors.

The group, directed Dr. Barbara Stanley, includes the Developing Center on Interventions for the Prevention of Suicide. In addition to serving as a special consultant to the VA in their development of interventions for veterans who are at risk for suicide, Dr. Stanley is PI on a number of studies underway:

- a randomized controlled study of the treatment of suicidal behavior and self-mutilation in BPD, which compares the efficacy of a six-month trial of Dialectical Behavior Therapy (DBT) vs. fluoxetine and medication management in the decrease of suicidal and self-harm behaviors

- two studies of treatment engagement of suicidal individuals in the emergency department

- a study examining the relationship between childhood neglect and suicidal behavior in BPD.

Training: The group is actively engaged in the training of psychiatry residents, psychology interns and psychology externs. Dr. Stanley conducted a course on suicide risk assessment and safety planning for PGY II's. Drs Stanley and Brodsky conducted a four-session course on DBT on the Intensive Outpatient Program. There is a year-long externship program in which three psychology doctoral students per year learn assessment and research methods in suicide intervention studies, and they learn how to and conduct DBT.

Neuropharmacology: Studies in this group concentrate on the role played by serotonin (5-HT) and a major receptor 5-HT_{1A} in contributing to the survival of cells in the brain of suicide victims and comparing them to matched controls. To better understand the intracellular transduction pathway downstream of the 5-HT_{1A} receptor, researchers have studied, in parallel, a cell line that expresses this receptor and revealed the "cross talk" between the various pro- and anti-apoptotic molecules that contributed to the delicate equilibrium between the competing pathways.

The study of CHO cells that stably express the 5-HT_{1A} receptor continues and activation or inhibition of this receptor revealed the involvement of X-linked inhibitor of apoptosis (XIAP), and Bax migration to the mitochondria as steps in the release of cytochrome C and apoptosis. Data suggest a central role of cAMP/PKA-dependent phosphatase (PP2A) in shifting the homeostasis of intracellular signaling downstream of 5-HT_{1A} receptor toward cell death in biological systems linked to neuropsychiatric disorders. Studies of postmortem tissue of suicide depressed victims and suicide schizophrenia victims compared to matched controls continued and the results of area B9 are being analyzed now.

In addition, in view of recent studies that indicate advances in the field of central oxytocinergic system that provided new insight from human and animal studies into the therapeutic potential of modulating this system for the treatment of human CNS disorders (eg anxiety, schizophrenia, autism), The group has studied the oxytocinergic

system and its development in preparation for studies in postmortem tissue of depressed suicide to assess the levels of oxytocin receptor. The technique applied in the current study using the peripheral nervous system will be used to study human post-mortem tissue).

Human Genetics and Neurochemistry: Dr. John Mann and Yung-yu Huang have been studying CSF monoamine metabolites and other neurotransmitter systems including peptides such as CRF corticotrophine releasing factor and substance P, GABA and glutamate in humans in collaboration with Dr. Tom Cooper. Studies of genetic and rearing effects on neurotransmitter levels in CSF and on the behavior in non-human primates are also conducted in collaboration with Drs. Jay Kaplan (Bowman Gray), Jeffrey Rogers (Southwestern Foundation), Cliff Jolly (NYU) and Lynn Fairbanks (UCLA). With Drs. Haghghi, Terwilliger, Gilliam, Russo and Goldman, candidate genes such as 5-HTR1A, 5-HTR1B, 5-HTR2A, HTT and TPH1 and TPH2 are being studied in postmortem brain tissue and blood or saliva samples from families and unrelated patients and controls to examine genetic and environmental effects on the brain and psychopathology with conventional and advanced DNA microarray techniques. Dr. Haghghi has two NIH grants to study genome-wide methylation patterns in mood disorders and mapping these effects onto candidate gene loci identified by SNP and expression arrays. Dr. Mann is Principal Investigator on an NIMH-funded international, multi-center GWAS of suicidal behavior in major depression.

Epigenomics: Dr. Victoria Haghghi and her group investigate the epigenetic basis of neuropsychiatric disorders with specific focus on major depressive disorder (MDD). Epigenetic processes may play an important role in the etiology of neuropsychiatric disorders, perhaps as equally important as genetics. One such epigenetic process is DNA methylation. Until recently epigenetics has received very little attention, yet there are likely pathological abnormalities in genomic methylation patterns that regulate genes involved in the development or physiology of the brain. In order to better understand both the wild type genomic DNA methylation patterns and aberrant methylation events that occur in disease states, her laboratory, in collaboration with Dr. Timothy H. Bestor, have developed a cost-effective, unbiased, whole-genome methylation profiling technique that can assay the methylation state of more than 80% of the CpG sites in the human genome. Using this methodology, which couples advances in next generation sequencing with enzymatic fractionation of DNA by methylation state, Dr. Haghghi is mapping the methylation at high coverage in a pilot study of controls and major depression cases. The study focuses on the prefrontal cortex (PFC) due to converging evidence from neuroimaging and functional studies implicating this region in MDD. In the first genome-wide DNA methylation profiling study of major depression, she identified aberrant methylation at several genes including those related to serotonergic and cholinergic pathways, neurotransmitter release, receptor functioning, and synaptogenesis. Subsequent to bisulfite sequencing validation of these differentially methylated regions, she will be expanding the analysis of these regions to a large sample of PFC tissue from sixty controls and MDD cases with comprehensive clinical and toxicological profiles. These DNA methylation abnormalities

may have clinical utility as biomarkers, and evaluation of the frequency of these alterations may help identify etiologic factors involved in MDD.

Laboratory of Molecular Neuroanatomy and the Diane Goldberg Laboratory for Molecular Imaging of Neural Disorders:

Dr. Victoria Arango and her colleagues conduct postmortem studies of suicide victims and alcoholics that utilize a combination of quantitative receptor autoradiography, in situ hybridization histochemistry and morphometric analysis of forebrain and brainstem nuclei. Her collaborators are Drs. Mark Underwood, Hadassah Tamir, John Mann, Helene Bach-Mizrachi and Maura Boldrini, as well as Suham Kassir and Yung-yu Huang. Drs. Arango, Dwork and Rosoklija direct the Brain Bank of the Conte Center for the Neuroscience of Mental Disorders. All cases, now collected in the Republic of Macedonia, undergo a detailed psychological autopsy, a toxicological screen including brain and hair analyses and neuropathological examination. In addition to demonstrating that suicide victims do not have fewer serotonin-synthesizing neurons or processes in the dorsal raphe nucleus, Dr. Arango and colleagues showed an increase in the level of tryptophan hydroxylase (TPH) protein and mRNA in the brainstem of suicide victims.

Using 3-D stereology, they found decreased neuronal density in the orbital, but not in the dorsal prefrontal cortex of suicide victims. They derived a binding index; the ratio of receptor binding to neuron density (fmol/mg tissue)/ (neurons/mm³) 5-HT_{1A} and 5-HT_{2A} binding indices were higher in orbital cortex in the suicide group, but were not different in BA9. These results lend support to a serotonergic abnormality in the ventrolateral prefrontal cortex of the brains of suicide victims, while the dorsolateral prefrontal cortex is largely spared.

Taken together, these studies revealed fundamental neurochemical differences between suicide victims and mood disorder patients. They indicate that morphological differences between controls and suicides are primarily confined to the ventral prefrontal cortex, while the dorsal prefrontal cortex remains largely unaffected. A collaboration with Dr. Lisanby, examines the neuroanatomical effects of electroconvulsive therapy and magnetic seizure therapy in nonhuman primates, including the examination of cell proliferation in the hippocampal formation following these seizure-inducing interventions. Other collaborations of Dr. Arango include postmortem studies of the cannabinoid 1 receptor with Dr. Vinod Yaragudri and Appa Hungund from the Nathan Kline Institute and molecular biology studies with Charles Glatt from Weill-Cornell. Dr. Arango also collaborates with Dr. Fatemeh Haghighi on a methylation study in depression and with Dr. Gil Zalsman on a SNP study of depression and suicide. These various projects are supported by the National Institute of Mental Health (NIMH), National Institute on Alcohol Abuse and Alcoholism (NIAAA), The Stanley Medical Research Institute, and the American Foundation for Suicide Prevention (AFSP) for postmortem human brain research. A postdoctoral research fellow soon-to-be-appointed assistant professor Dr. Boldrini has secured NIH funding in the form of an R01 to study neurogenesis in postmortem human. . Drs. Boldrini and Bach-Mizrachi, have all secured AFSP and NARSAD awards.

Dr. Bach-Mizrachi's research focus has centered on understanding the role of the serotonin biosynthetic enzyme, neuronal tryptophan hydroxylase (TPH2) in regulating brain serotonin in the context of major depressive disorder and suicide. Using postmortem brainstem tissue of depressed suicides, Dr. Bach-Mizrachi has shown elevated TPH2 transcript expression in comparison to controls in the serotonergic source neurons in the dorsal and median raphe nuclei. This finding suggests a compensatory up-regulation of the serotonergic system resulting from the deficits in serotonin in suicides. Dr. Bach-Mizrachi now aims to understand the molecular mechanisms involved in regulating TPH2 expression and function. Her current research focuses on measuring the expression and function of components of the TPH2 modulating, PKA and GSK3 β signal transduction pathways in postmortem tissue of suicides and controls. While concentrating on the molecular biology of suicide, Dr. Bach-Mizrachi has expanded her research studies into related disorders including alcoholism and schizophrenia. In so doing, Dr. Bach-Mizrachi is conducting comparative studies in the prefrontal cortex of depressed suicides, schizophrenic suicides and matched controls, in which TPH2 and post-translational modifications of TPH2 are measured. In alcoholics, Dr. Bach-Mizrachi has recently received funding from NIAAA to elucidate the role and interaction of TPH2 and GABA in the postmortem brainstem of alcoholics and matched controls. In summary, Dr. Bach-Mizrachi has taken a molecular approach to understanding the role and regulation of TPH2 in psychiatric disorders where serotonin neurotransmission is deficient.

Another new area of research in Dr. Arango's group is in the area of neurogenesis. The effort is led by Dr. Boldrini, who has been working on a project for the study of the effect of major depression and antidepressants on human neurogenesis. The preliminary data characterized human adult neurogenesis in normal subjects and individuals with mood disorders and suicide and showed a pronounced effect of antidepressant treatment increasing human adult neurogenesis. Preliminary work was conducted in Dr. Arango's laboratory while Dr. Boldrini was the Paul Janssen Fellow in Translational Neuroscience and produced the preliminary data for three successful applications for: 1) a New York State Stem Cell Initiative (NYSTEM) grant (R Hen/V Arango Co-PIs), "Hippocampal stem cells and depression"; 2) an NIMH R01 MH083862-01 (Boldrini, PI) "Effect of Major Depression and antidepressants on human neurogenesis"; and 3) an American Foundation for Suicide Prevention grant (Boldrini, PI), "The effect of suicide on hippocampal neuron number in humans."

Dr. Boldrini also carried out a study assessing the amount of tryptophan hydroxylase (TPH) protein in the dorsal raphe nucleus (DRN) in subjects with bipolar disorder, major depression, Schizophrenia and non-psychiatric controls with and without suicide. This research was supported by a grant from NARSAD.

Serotonergic Neuron Morphometry: Dr. Mark D. Underwood conducts research into the regulation of serotonergic neurons in the dorsal raphe nucleus in the postmortem human brainstem in suicide and alcoholism. The studies examine serotonergic neurons directly and define their functional capacity using quantitative morphometric and receptor binding methods. These studies are supported by the NIH (R01 AA11293 M.

Underwood, PI; R01 MH40210, V. Arango, PI). Dr. Underwood and colleagues are also performing translational studies examining gene-environment interactions and effects on the development of the serotonergic system in the brain of transgenic mice and how this affects behavior in a project in the Conte Center for the Neuroscience of Mental Disorders (P50 MH62185, J. John Mann, PI). He chairs the Columbia University Medical Center Institutional Animal Care and Use Committee (IACUC).

Neuropathology of Psychosis, Alzheimer's Disease and Other Major Psychiatric Disorders: Dr. Andrew Dwork and colleagues study neuropathological features of schizophrenia and mood disorders, and neuropathological correlates of the dementia that is common among elderly individuals with schizophrenia. Current projects include:

- Structural abnormalities of dendrites in schizophrenia, mood disorders, and animal models of these illnesses and their treatments. These studies employ the group's NeoGolgi method of neuronal impregnation, which is the first to provide predictable and uniform Golgi impregnations. Animal studies are conducted in collaboration with Drs. Jeremy Coplan, Jay Gingrich, Sarah Lisanby, Holly Moore, Tarique Perera, Lorna Role, and David St Clair
- Histological and biochemical studies of white matter and myelin in schizophrenia, depression, and suicide
- Collection of brains and clinical data from autopsies of psychiatric patients, suicides, and comparison cases in the Republic of Macedonia. Material from this collection is employed in numerous studies within the Division and in collaboration with other departments and institutions
- A historical study using the ecological introduction of neuroleptic drugs to determine the effect of the duration of untreated psychosis on the course of schizophrenia after the initiation of antipsychotic treatment
- Studies of the role of neurogenesis in the response of animal models of depression to antidepressant treatments
- A multi-laboratory collaboration, organized by Dr. Alan Brown in the Division of Epidemiology, to investigate abnormalities of microtubules in schizophrenia and animal models of schizophrenia.

Three new grants were awarded to the laboratory during this period: R21 MH082395 (Rosoklija), "Morphology of Hippocampal Neurons in Depression"; R21 TW008058 (Rosoklija), "A Macedonian Center for EM Studies of Schizophrenia"; NARSAD Independent Investigator Award (Dwork), "Subicular Region Association Fibers in Development and Schizophrenia."

Brain Imaging: Dr. Ramin V. Parsey is the Director of the Brain Imaging Core. Dr. Todd Ogden is the senior brain image analysis statistician. He has developed novel innovations in methods and software for kinetic modeling and analysis of PET

neuroreceptor binding studies. Dr. Ogden, together with the kinetic modeling expertise of Dr. Ramin Parsey and the programming skills of Dr. Ashish Ojha, has developed a new voxel-based image analysis routine.

The Core continues to study major depression and bipolar depressed subjects before and after treatment with an SSRI or ECT, suicide attempters and non-attempters, anxiety disorders and healthy volunteers. These studies have generated important new data that for the first time demonstrate that many of the group's findings in postmortem human brain tissue can be detected in vivo in depressed subjects. Abnormalities detected in currently depressed subjects are now being investigated in remitted depressed subjects in an effort to determine if biological abnormalities are state or trait phenomena.

Dr. Matthew Milák has just started the third year of his NIMH sponsored Career Development Award (K08), "Characterization of a Novel 5-HT_{1A} Receptor Agonist PET Ligand." In the context of this award he has been studying [¹¹C]CUMI-101 (first agonist serotonin 1A receptor positron emission tomography ligand) in both animal and human scans to establish this radiotracer's reliability and reproducibility. Dr. Milák is currently working on testing the hypothesis that [¹¹C]CUMI-101 is sensitive to changes in brain intra-synaptic serotonin levels in humans, a hypothesis he has proven in an animal model. Dr. Milák is also working on two studies sponsored by NARSAD. The first one is concerned with finding and developing brain imaging assays detecting biochemical changes of depressive susceptibility that can serve as a trait marker in yet healthy offspring of major depressive disorder patients. The second one is testing the mechanism of action of a novel treatment for depression that can relieve the symptoms of major depressive disorder in two to three hours.

Dr. Elizabeth Sublette has an AFSP, NARSAD, Clinical and Translational Science Award (CTSA), and NIMH funding for studies comparing relationships between plasma polyunsaturated fatty acid levels and brain functioning in depressed subjects (including suicide attempters and non-attempters) and healthy volunteers.

Dr. Arno Klein has concluded a study comparing 15 different brain registration methods with the following coauthors/participants from around the world: Jesper Andersson, Babak Ardekani, John Ashburner, Brian Avants, Ming-Chang Chiang, Gary Christensen, Louis Collins, Pierre Hellier, Hyun Song Joo, Mark Jenkinson, Claude Lepage, Daniel Rueckert, Paul Thompson, Tom Vercauteren, and Roger Woods. After having conducted over 45,000 brain-to-brain registrations using these methods, it was possible to determine which methods perform more accurate registrations by brain region according to volume overlap, surface overlap, volume similarity, and distance error measures. This information is generally useful to the neuroscience community, and is of particular interest to the Division because Dr. Klein will integrate the best method in a new version of the Mindboggle software package for automated anatomical labeling of brain image data.

The group collaborates on NIH funded imaging studies with Dr. Davangere Devanand, Chief of the Division of Geriatrics, Dr. Evelyn Attia in Eating Disorders, Dr. Richard Sloan in Consultation Liaison Psychiatry, Drs. Paul Harris and Rudi Liebel in Diabetes (NewYork Presbyterian Hospital), and Dr. Yaakov Stern in Cognitive Neuroscience. Funding has been provided for occupancy studies with new therapeutic agents and for development of novel PET tracers for new molecular targets. Ongoing funding from NIMH include the Conte Center for the Neuroscience of Mental Disorders: The Study of Suicidal Behavior, R01 grants, a NIH K01 award, NIMH K08 grants, American Foundation for Suicide Prevention grants, Clinical Trials Office, Dana Foundation and NARSAD grants.

Dr. Peter Freed received an NIMH grant to study grief process with fMRI. He works with Drs. Mann, Hirsch and Bonano on this project.

PET Chemistry: Dr. Dileep Kumar is the head of PET chemistry, which includes Drs. Jaya Prabhakaran and Vattoly Majo and Mr. Norman Simpson who are outstanding organic chemists and radiochemists. As a result of their expertise, this group performed a number of human studies successfully with the first PET agonist radiotracer for the 5-HT_{1A} systems, CUMI-101. Dr. Kumar and colleagues believe that [C-11]CUMI has the potential to image a variety of neuropsychiatric and neurodegenerative diseases. The kappa opioid agonist tracer [C-11]GR103545 was successfully launched for human studies for the first time in collaboration with Dr. Diana Martinez.

Neuropsychology: Dr. John G. Keilp and colleagues investigate cognitive and behavioral characteristics of individuals with depression and suicidal behavior with a goal of understanding their role in the pathophysiology of these disorders. Data are linked to clinical, imaging, and biochemical measures collected by the group. Data have been used to characterize individuals with suicide attempt histories, understand the role of executive dysfunction in violent suicide attempts, and for the prediction of later treatment response and suicide attempt risk. The laboratory continues its collaborations with geriatric psychiatry and the Lyme Disease Research Center.

They are currently using fMRI to examine the underlying cortical mechanisms of deficits in cognitive control. There are ongoing studies of stress response using a social stress paradigm to evaluate functioning of arousal systems and their role in depression, suicidal behavior, and cognitive dysfunction. In addition, they are examining the feasibility of using single-dose drug challenge paradigms and their effects on behavior and neuroendocrine function for the prediction of treatment response and suicide attempt risk.

Statistics and Data Management: In the last year, Dr. Hanga Galfalvy has focused on refining her clinical prediction model for prospective suicide attempts and on research of biological predictors of suicide attempts. She has published in *Acta Psychiatrica Scandinavica* a first-author research paper on the validation of predictive models for suicide attempt, co-authored an extensive paper comparing the correlates of suicidal behavior in the two bipolar subtypes and was the co-author of two other papers

about the genetic and morphological correlates of depression and suicide. Dr. Galfalvy has presented a poster at the Annual Meeting of the Society of Biological Psychiatry on the association between cerebrospinal fluid levels of the noradrenaline metabolite MHPG and short-term suicide risk as well as started a re-analysis of existing data on predictors of prospective suicide attempts by the timing of the attempt, separating immediate attempts from later ones, to study models that predict short term vs. long term risk of suicide attempt. In addition, she has consulted with division researchers on several projects, including completion of the analysis for two studies, substantial statistical help for a third paper on the genetic associates of suicidal behavior, and analysis of data on genetic and social resilience factors that influence the risk of remission and relapse in patients suffering a major depressive episode.

Division head Dr. Steven Ellis continued to develop statistical methods for prediction of suicide attempts. He presented the paper "Some issues in suicide attempt prediction" at the International Biometric Society, Eastern North American Region Spring meeting. He has continued to develop a "machine learning" algorithm for suicide attempt prediction and he presented the poster "Kernel based decision theoretic survival analysis with emphasis on prediction" at the New York Academy of Sciences, Symposium on Machine Learning. Much of his remaining effort during the year focused on refining and writing up his algorithm for convex optimization, a key component of his prediction method.

New Grants

American Foundation for Suicide Prevention

Dr. Helene Bach-Mizrachi, "Expression of a Truncated Isoform of Neuronal Tryptophan Hydroxylase in the Brainstem of Depressed Suicides"

Dr. Maura Boldrini, "The Effect of Suicide in Hippocampal Neuron Number in Humans"

Dr. Eric Fertuck, "Cortisol Reactivity in the Prediction of Suicide Attempts in Borderline Personality Disorder"

Dr. Marianne Gorlyn, "Neuropsychological Predictors of Antidepressant Treatment Response in Suicide Attempters"

Dr. Barbara Stanley, "The Impact of Childhood Neglect on Suicidal Behavior" and "Systematic Classification of Suicidal Behavior"

Irving Institute CTSA Pilot Award

Dr. Jeffrey Miller, "PET imaging of the serotonin system to predict treatment outcome with cognitive behavioral therapy for depression"

National Alliance for Research on Schizophrenia and Depression (NARSAD)

Dr. Marianne Gorlyn, “Aggressive Behavior in Depression and Suicide: Biochemical, Behavioral, and Cognitive Aberrations in the Stress Response”

Dr. John Keilp, “Localization of Selective Attention Deficits in High Lethality Suicide Attempters”

Dr. Jeffrey Miller, “Young Investigator Award for work using functional MRI to predict treatment response in major depressive disorder”

National Institute on Alcohol Abuse and Alcoholism

Dr. Helene Bach-Mizrachi, “Integrative Neuroscience Initiative on Alcoholism, Role of Neuronal Tryptophan Hydroxylase in Alcoholism”

Dr. Mark Underwood, “Serotonergic Neurons in Alcoholism” (Five year competitive renewal)

National Institutes of Health

Dr. Victoria Arango, “5-HT1A receptor anti-apoptotic transduction pathways in suicide (Y01-05)” (R01)

National Institute of Mental Health

Dr. Maura Boldrini, “Effect of Major Depression and Antidepressants on Human Neurogenesis (Y01-Y05)” (R01)

Dr. Fatemeh G. Haghghi, “Suicidal Behavior in Mood Disorder; Genes & Intermediate Phenotype” (R01)

New York Stem Cell Science (NYSTEM)

Dr. Victoria Arango (Co-Principal Investigator), “Institutional Development of Stem Cells Research capabilities”

Simons Foundation

Dr. Fatemeh G. Haghghi, “Simons Foundation Autism Research Initiative”;
Co-Investigator, “Identification of Aberrantly Methylated Genes in Autism: The Role of Advanced Paternal Age”

Veteran’s Administration

Dr. Barbara Stanley, “Safety Planning in Emergency Settings with Suicidal Veterans”

Awards/Honors

Dr. Victoria Arango became a member of several professional committees in 2007: the CoAP Committee, New York State Psychiatric Institute, the Research Grants Committee of the American Foundation for Suicide Prevention and the Program Committee of the Society for Biological Psychiatry. She was appointed for a second term on the Credential Committee of the American College of Neuropsychopharmacology.

Dr. Christine DeLorenzo received a Columbia University Fellowship for Research Training in Affective, Anxiety, Eating & Related Disorders in 2008.

Dr. Eric Fertuck received the John Weber Award for Research, Columbia University Center for Psychoanalytic Training and Research in 2008.

In 2008, Dr. Todd Ogden was presented with a Glenda Garvey Teaching Academy Fellowship (Columbia University Medical Center) and received the HO Hartley Award for distinguished service to the discipline of statistics.

Dr. Maria A Oquendo was named Vice Chair for Education in 2007 and Residency Training Director in 2008. She was appointed Fellow of the APA in 2008 and elected President of the American Society of Hispanic Psychiatry, effective 2009. In addition, she was named chairwoman of the American Psychiatric Association (APA) Substance Abuse and Mental Health Services Administration (SAMHSA) Fellowship Selection Committee in 2008 and became a member of the APA Committee on Research Training also in 2008.

Dr. Ramin V Parsey was awarded the AE Bennett Research Award for Basic Science by the Society of Biological Psychiatry in 2008.

Dr. Barbara Stanley was appointed to the American Psychological Association Presidential Task Force on IRBs and Psychological Research. She was also appointed President of the Metropolitan NY Chapter of the American Foundation for Suicide Prevention.

Dr. Mark Underwood continues to serve as the Chair of the Institutional Animal Care and Use Committees (IACUC) at the Columbia University Medical Center.

Dr Scott Wilson received the Association for Research in Personality Disorders Student Research Award and the National Education Alliance for Borderline Personality Disorder Young Investigator Award, both in 2008.

Highlights

For the first time, the Brain Imaging laboratory developed a novel agonist radiotracer, [11C]CUMI-101, to image high affinity serotonin 1A receptors, in people. This is believed to be the first PET tracer developed from scratch for use in people at the institution. PET scan serotonin studies indicate that remission at three or twelve months is related to scan findings at baseline suggesting that PET scanning may predict antidepressant response.

The Mood Disorders & Suicide Risk Clinical Research group had more than thirty publications listed in PubMed in academic year 2007-2008. Some of the most salient reports cover: a classification system for suicidal behavior; the effects of comorbid alcoholism in bipolar disorder; protective factors for suicidal behavior in mood disorders; and a pharmacologic challenge as a marker of future suicidal behavior. In addition, the group continues to receive trainees and visiting faculty from all over the world. Dr. Jeronimo Saiz-Ruiz, Chairman at the Universidad de Alcala, spent his sabbatical with the clinical group. Dr. Lena Nabuco Abreu, Assistant Professor at the Universidad de Sao Paulo, and Dr. Maria Dolores Braqueais from the University of Barcelona spent five months and six months, respectively, training with the group.

The Personality Disorders group has published more than twenty articles in the past academic year focusing predominantly on the intersection of borderline personality disorder and suicidal behavior. Specifically, the group addressed the interpersonal dysfunction associated with borderline personality disorder from a neurocognitive, biological, and treatment perspective. This aspect of borderline personality disorder has been relatively neglected yet there is evidence that it plays a crucial role in the disorder. They have learned that interpersonal triggers are prominent in suicidal behavior for individuals with borderline personality disorder and that social stress reactivity of the hypothalamic pituitary axis was heightened in suicide attempters with borderline personality disorder. Relevant candidate genes and gene x environment interactions are being studied.

Studies in the Neuropharmacology group have demonstrated that activating the 5-HT_{1A} receptor increases the levels of the transcription factor NFκB, which can promote cell survival by increasing the X-linked inhibitor of apoptosis protein (XIAP) expression. Thus, XIAP is a novel and critical target of 5-HT_{1A} activation. Considering that neuropsychiatric disorders may involve neurodegenerative processes, it will be important to examine possible XIAP expression levels in future studies of post-mortem tissue. Studies in this group provide a better understanding of imbalance between pro- and anti-apoptotic proteins as possible risk factors leading to "neuroendangerment" in major depression, suicide and other neuropsychiatric disorders (Hsiung et al, 2008).

The neuropsychology group completed a five-year study of neurocognitive factors and their association to suicidal behavior, finding that deficits in cognitive control mechanisms are a strong correlate of past attempt status.

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2007

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