BIOGRAPHICAL SKETCH

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NAME: **J. John Mann, M.D.**

eRA COMMONS USER NAME (credential, e.g., agency login): JOHNMANN

POSITION TITLE: The Paul Janssen Professor of Translational Neuroscience (in Psychiatry & Radiology); Research Scientist VIII

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Melbourne University, Australia	M.B., B.S.	12/1971	Medicine
Royal Australasian Coll. Physicians, Australia	FRACP Pt1	10/1974	Internal Medicine
Melbourne University, Australia	D.P.M.	12/1976	Psychiatry
Melbourne University, Australia	M.D.	12/1978	Neurobiology

A. Personal Statement:

Dr. Mann is internationally renowned for his research into the neurobiology of the brain and monoamine and peptide neurotransmitters. He has played a central role in the conception and preparation of this application. It builds directly on PET and NIRS research studies of the inflammasome in mood disorders that he has conducted often in collaboration with Dr. Sublette. He will chair research meetings and supervise subject recruitment, brain imaging and analyses to monitor progress in meeting research goals. He will attend weekly subject recruitment meetings, weekly brain imaging review meetings where scans from the previous week are reviewed for quality control purposes and weekly image data cleaning and analysis meetings. He will contribute to manuscript preparation. He and Dr. Sublette will participate with key research staff in weekly or biweekly teleconferences to review progress, monitor data transfer, review progress on publication plan and resolve all details of protocol conduct.

B. Positions and Honors (since 1988):

1988 - 1989 Professor of Psychiatry, Cornell University Medical College, New York, NY
1989 - 1994 Professor of Psychiatry, University of Pittsburgh, Pittsburgh, PA
1994 - 1997 Professor of Psychiatry, College of Physicians & Surgeons at Columbia University, NY
1994 - Director, Molecular Imaging & Neuropathology Division, Dept. of Psychiatry at New York State Psychiatric Institute, New York, NY
1997 - 2005 Professor of Psychiatry & Radiology, Coll. of Physicians & Surgeons at Columbia University, NY
2005 - The Paul Janssen Professor of Translational Neuroscience (in Psychiatry & Radiology), Columbia University, New York, NY

C. Contribution to Science

1. *Positron emission tomography in mood disorders.* My work in the neurobiology of mood disorders has encompassed PET studies using a number of radiotracers, including FDG, serotonergic and other neurotransmitter system radioligands.

   a. Parsey RV, Oquendo MA, Zea-Ponce Y, Rodenhiser J, Kegeles LS, Pratap M, Cooper TB, Van Heertum R, Mann JJ, Laruelle M. Dopamine D2 receptor availability and amphetamine-induced

dopamine release in unipolar depression. *Biol Psychiatry.* 2001 Sep 1;50(5):313-322. PMID: 11543733

b. Sublette ME, Milak MS, Hibbeln JR, Oquendo MA, Malone KM, Parsey RV, Mann JJ. Plasma polyunsaturated fatty acids and regional cerebral glucose metabolism in major depression. *Prostaglandins Lukot Essent Fatty Acids.* 2009; 80(1): 57-64. PMID: 19128951 PMC2712826

c. Miller JM, Hesselgrave N, Ogden RT, Sullivan G, Oquendo MA, Mann JJ, Parsey RV. Positron emission tomorgraphy quantification of serotonin transporter in suicide attempters with major depressive disorder. *Biol Psychiatry* 2013 Aug 15;74(4):287-295 PMID: 23453288 PMC3725207

d. Oquendo MA, Hastings RS, Huang YY, Simpson N, Ogden RT, Hu, XZ Goldman D, Arango V, Van Heertum RL, Mann JJ, Parsey RV. Brain serotonin transporter binding in depressed patients with bipolar disorder using positron emission tomography. *Arch Gen Psychiatry.* 2007 Feb;64(2):201-208. PMID: 17283287

2. *PET Studies of 5-HT!A Autoreceptors in Mood Disorders.* Dr. Mann designed and with his colleagues and team has conducted a series of studies showing elevated binding is a trait associated with major depression and transmitted in families.

a. Parsey RV, Oquendo MA, Ogden RT, Olvet DM, Simpson N, Huang YY, Van Heertum R, Arango V, Mann JJ. Altered serotonin 1A binding in major depression: a [carbonyl-C-11]WAY100635 positron emission tomography study. Biol Psychiatry. 2006;59(2):106-13

b. Miller JM, Brennan KG, Ogden TR, Oquendo MA, Sullivan GM, Mann JJ, Parsey RV. Elevated serotonin 1A binding in remitted major depressive disorder: evidence for a trait biological abnormality. Neuropsychopharmacology. 2009;34(10):2275-84

c. Parsey RV, Ogden RT, Miller JM, Tin A, Hesselgrave N, Goldstein E, Mikhno A, Milak M, Zanderigo F, Sullivan GM, Oquendo MA, Mann JJ. Higher serotonin 1A binding in a second major depression cohort: modeling and reference region considerations. Biol Psychiatry. 2010;68(2):170-8

d. Milak MS, Pantazatos S, Rashid R, Zanderigo F, DeLorenzo C, Hesselgrave N, Ogden RT, Oquendo MA, Mulhern ST, Miller JM, Burke AK, Parsey RV, Mann JJ. Higher 5-HT1A autoreceptor binding as an endophenotype for major depressive disorder identified in high risk offspring - A pilot study. *Psychiatry Res Neuroimaging.* 2018;276:15-23

3. *Action of Antidepressants.* I have studied multiple aspects of the action of antidepressants on the neurobiology of mood disorders

a. Parsey RV, Olvet DM, Oquendo MA, Huang YY, Ogden RT, Mann JJ. Higher 5-HT_{1A} receptor binding potential during a major depressive episode predicts poor treatment response: preliminary data from a naturalistic study. *Neuropsychopharmacology.* 2006 Aug;31(8):1745-1749. PMID: 16395308

b. Miller JM, Oquendo MA, Ogden RT, Mann JJ, Parsey RV. Serotonin transporter binding as a possible predictor of one-year remission in major depressive disorder. *J Psychiatr Re*s. 2008 Oct; 42(14):1137-1144. PMID: 18331740 PMC2670200

c. Boldrini M, Underwood MD, Hen R, Rosoklija GB, Dwork AJ, Mann JJ, Arango V. Antidepressants increased neural progenitor cells in the human hippocampus. *Neuropsychopharmacology.* 2009;34(11): 2376-2389. PMID: 19606083 PMC2743790

d. Gray NA, Milak MS, Delorenzo C, Ogden RT, Huang YY, Mann JJ, Parsey RV. Antidepressant treatment reduces serotonin-1A autoreceptor binding in major depressive disorder. Biol Psychiatry 2013;74(1):26-31. PMID: 23374637 PMCID:PMC3690146

4. Neurobiology of Mood Disorders: Dr. Mann has studied brain abnormalities more generally in mood disorders.

a. Sublette ME, Galfalvy HC, Hibbeln JR, Keilp JG, Malone KM, Oquendo MA, Mann JJ. Polyunsaturated fatty acid associations with dopaminergic indices in major depressive disorder. Int J Neuropsychopharmacol. 2014 Mar;17(3):383-391. PMID: 24300434 PMCID:PMC3956108

b. Haghighi F, Galfalvy H, Chen S, Huang YY, Cooper TB, Burke AK, Oquendo MA, Mann JJ, Sublette ME. DNA methylation perturbations in genes involved in polyunsaturated Fatty Acid biosynthesis associated with depression and suicide risk. Front Neurol. 2015 Apr 28;6:92. doi:10.3389/fneur.2015. 00092. eCollection 2015 PMID:25972837 PMCID:PMC4412056

c. Sublette ME, Galfalvy HC, Fuchs D, Lapidus M, Grunebaum MF, Oquendo MA, Mann JJ, Postolache TT. Plasma Kynurenine levels are elevated in suicide attempters with major depression disorder. *Brain Behav Immun.* 2011 Aug;25(6):1272-1278. PMID: 21605657
d. Boldrini M, Santiago AN, Hen R, Dwork AJ, Rosoklija GB, Tamir H, Arango V, John Mann J. Hippocampal granule neuron number and dentate gyrus volume in antidepressant–treated and untreated major depression. Neuropsychopharmacology. 2013 May;38(6):1068-77 PMID: 23684624PMCID:PMC3679303

5. *NIRS Studies* Dr. Mann has worked with Dr. Holper on a series of NIRS studies.

a. Holper L, Mann JJ. Test–retest reliability of brain mitochondrial cytochrome-c-oxidase assessed by functional near-infrared spectroscopy. J. Biomed. Opt. 23(5), 056006 (2018), doi: 10.1117/1.JBO.23.5.056006
b. Holper L, Ben-Shachar D, Mann JJ. Multivariate meta-analyses of mitochondrial complex I and IV in major depressive disorder, bipolar disorder, schizophrenia, Alzheimer disease and Parkinson disease. *Neuropsychopharmacology* (In Press 7-May-2018).
c. Holper L, Ben-Shachar D, Mann JJ. Psychotropic and Neurological Medication Effects on Mitochondrial Complex I and IV in Rodent Models. ENP-18-326R1 - European Neuropsychopharmacology
d. Holper, L., Lan, M. J., Brown, P. J., Sublette, E. M., Burke, A., & Mann, J. J. (2019). Brain cytochrome-c-oxidase as a marker of mitochondrial function: A pilot study in major depression using NIRS. *Depression and Anxiety*. 1-14.

1. <u>*Computational psychiatry and fMRI studies*</u>**:**
   a. **Pantazatos SP,** Talati A, Pavlidis P, Hirsch J. Decoding unattended fearful faces with whole-brain correlations: an approach to identify condition-dependent large-scale functional connectivity. PLoS Comput Biol. 2012;8(3):e1002441. PMID: 22479172; PMC3315448.
   b. **Pantazatos SP**, Talati A, Pavlidis P, Hirsch J. Cortical functional connectivity decodes subconscious, task-irrelevant threat-related emotion processing. Neuroimage. 2012 Jul 16;61(4):1355-63. PMID: 22484206; PMC3393600.
   c. **Pantazatos SP**, Talati A, Schneier FR, Hirsch J. Reduced anterior temporal and hippocampal functional connectivity during face processing discriminates individuals with social anxiety disorder from healthy controls and panic disorder, and increases following treatment. Neuropsychopharmacology. 2014 Jan;39(2):425-34. PMID: 24084831; PMC3870777.
   d. Lan MJ, Rizk MM, **Pantazatos SP**, Rubin-Falcone H, Miller JM, Sublette ME, Oquendo MA, Keilp JG, Mann JJ. Resting-state amplitude of low-frequency fluctuation is associated with suicidal ideation. Depress Anxiety. 2019 May;36(5):433-441. PMID: 30900329; PMCID: PMC6488362

2. <u>*Suicide, bioinformatics and computational genomics:*</u> As a Paul Janssen Translational Neuroscience Postdoctoral Research Fellow in the CU Dept. of Psychiatry and a K01 Award Trainee, I acquired training in psychiatric genomics and contributed bioinformatics analyses (RNA-seq) to examine postmortem brain gene expression differences in suicide and major depression. In (a) we replicate the finding of lower spermidine/spermine N1-Acetyltransferase1 (SAT1) brain gene expression and characterize isoform-level differences in suicide. We applied an integrated functional genomics approach (combining brain gene expression, eQTL analyses, and DNA structural variation) to examine glutamate/GABA systems (b) and glucorticoid-receptor related genes (c) in suicide and depression. In (d) we applied a whole-transcriptome profiling to identify putative genes, pathways and splicing events altered in suicide and depression.
   a. **Pantazatos SP**, Andrews SJ, Dunning-Broadbent J, Pang J, Huang YY, Arango V, Nagy PL, John Mann J. Isoform-level brain expression profiling of the spermidine/spermine N1-Acetyltransferase1 (SAT1) gene in major depression and suicide. Neurobiol Dis. 2015 Jul;79:123-34. PMID: 25959060; PMC4834874.
   b. Yin H, **Pantazatos SP**, Galfalvy H, Huang YY, Rosoklija GB, Dwork AJ, Burke A, Arango V, Oquendo MA, Mann JJ. A pilot integrative genomics study of GABA and glutamate neurotransmitter systems in suicide, suicidal behavior, and major depressive disorder. Am J Med Genet B Neuropsychiatr Genet. 2016 Apr;171B(3):414-26. PMID: 26892569; PMC4851346.
   c. Yin H, Galfalvy H, **Pantazatos SP**, Huang YY, Rosoklija GB, Dwork AJ, Burke A, Arango V, Oquendo

MA, Mann JJ. Glucocorticoid receptor-related genes: genotype and brain gene expression relationships to suicide and major depressive disorder. Depress Anxiety. 2016 Jun;33(6):531-40. PMID: 27030168; PMC4889464.

d. **Pantazatos SP**, Huang YY, Rosoklija GB, Dwork AJ, Arango V, Mann JJ. Whole-transcriptome brain expression and exon-usage profiling in major depression and suicide: evidence for altered glial, endothelial and ATPase activity. Mol Psychiatry. 2017 May;22(5):760-773; PMID: 27528462.

3. *Computational psychiatry, PET and structural neuroimaging*: In addition to fMRI-based studies, I have conducted and contributed analyses towards several structural MRI and PET studies. We identified grey matter volume differences in parahippocampus, temporal pole and cerebellum in two independent cross-sectional samples of social anxiety disorder and healthy volunteers (a), and we also identified grey matter volume changes associated with paroxetine treatment in social anxiety disorder (b). I showed that individual season of birth in adults is detectable with MRI, implying that birth season effects on the developing human brain persist through adulthood and suggesting that neuroimaging may be a valuable intermediate phenotype in bridging the gap between birth season and personality and neurobehavioral disorders (c). More recently I applied multi-voxel pattern analysis to 5HT1A PET scans to classify individuals at high risk for developing major depressive disorder (d).
    a. Talati A, **Pantazatos SP**, Schneier FR, Weissman MM, Hirsch J. Gray matter abnormalities in social anxiety disorder: primary, replication, and specificity studies. Biol Psychiatry. 2013 Jan 1;73(1):75-84. PMID: 22748614; PMC3465490.
    b. Talati A, **Pantazatos SP**, Hirsch J, Schneier F. A pilot study of gray matter volume changes associated with paroxetine treatment and response in social anxiety disorder. Psychiatry Res. 2015 Mar 30;231(3):279-85. PMID: 25659476; PMC4363180.
    c. **Pantazatos SP**. Prediction of individual season of birth using MRI. Neuroimage. 2014 Mar;88:61-8. PMID: 24246490; Central PMC4545475.
    d. Milak MS, **Pantazatos S**, Rashid R, Zanderigo F, DeLorenzo C, Hesselgrave N, Ogden RT, Oquendo MA, Mulhern ST, Miller JM, Burke AK, Parsey RV, Mann JJ. Higher 5-HT1A autoreceptor binding as an endophenotype for major depressive disorder identified in high risk offspring - A pilot study. 2018 Jun 30;276:15-23. PMID: 29702461; PMC5959803

4. *Integrative neuroinformatics and molecular neuroanatomy:* We examined the effects of spatial proximity on the relationship between gene expression and distributed spatial patterns of synchronous brain activity (i.e. canonical networks) consistently observed in resting state fMRI (a). The study also contributed methods to control for the confounding effects of spatial proximity on gene expression and functional connectivity patterns. I contributed analyses and interpretation for a recent study examining the transcriptomic correlates of structural MRI scans (b). These results provide a molecular characterization of MR contrast that will aid interpretation of future MR studies of the brain. In (c), I conducted voxel-wise regression analyses demonstrating altered relationships between 5-HT1A receptor binding and grey matter volume in depression.
    a. **Pantazatos SP**, Li X. Commentary: BRAIN NETWORKS. Correlated Gene Expression Supports Synchronous Activity in Brain Networks. Science 348, 1241-4. Front Neurosci. 2017 Jul 18;11:412. PMID: 28769750; PMC5513927
    b. Ritchie J, **Pantazatos SP**, French L. Transcriptomic characterization of MRI contrast with focus on the T1-w/T2-w ratio in the cerebral cortex. Neuroimage. 2018 Jul 1;174:504-517. PMID: 29567503
    c. Zanderigo F, **Pantazatos S**, Rubin-Falcone H, Ogden RT, Chhetry BT, Sullivan G, Oquendo M, Miller JM, Mann JJ. In vivo relationship between serotonin 1A receptor binding and gray matter volume in the healthy brain and in major depressive disorder. Brain Struct Funct. 2018 Jul;223(6):2609-2625

5. *Eating disorders and fMRI:* In collaboration with the Mt. Sinai/St. Luke's Roosevelt Obesity Research Center, I have contributed neuroimaging analyses to further understand the neural bases of eating behavior. We show reductions in reward-related regions in response to high energy dense (Hi ED) foods following bariatric surgery (a). We showed higher activation in limbic and dopaminergic-related regions in response to multimodal Hi ED food cues in obese individuals (b), and in (c) we show higher activation in response to multimodal Hi ED stimuli in anterior cingulate cortex in individuals with binge eating disorder. We also examined sex-differences in neural circuitry underlying food stimulus processing (d).
    a. Ochner CN, Kwok Y, Conceição E, **Pantazatos SP**, Puma LM, Carnell S, Teixeira J, Hirsch J, Geliebter A. Selective reduction in neural responses to high calorie foods following gastric bypass surgery. Ann Surg. 2011 Mar;253(3):502-7. PMID: 21169809; PMC3128512.

b. Carnell S, Benson L, **Pantazatos SP**, Hirsch J, Geliebter A. Amodal brain activation and functional connectivity in response to high-energy-density food cues in obesity. Obesity (Silver Spring). 2014 Nov;22(11):2370-8. PMID: 25098957; PMC4224976.
c. Geliebter A, Benson L, **Pantazatos SP**, Hirsch J, Carnell S. Greater anterior cingulate activation and connectivity in response to visual and auditory high-calorie food cues in binge eating: Preliminary findings. Appetite. 2016 Jan 1;96:195-202. PMID: 26275334; PMC4684801.
d. Atalayer D, **Pantazatos SP**, Gibson CD, McOuatt H, Puma L, Astbury NM, Geliebter A. Sexually dimorphic functional connectivity in response to high vs. low energy-dense food cues in obese humans: an fMRI study. Neuroimage. 2014 Oct 15;100:405-13. PMID: 24862077; PMC4138250

Complete List of Published Work:
http://www.ncbi.nlm.nih.gov/pubmed/?term=j+john+mann

D. Research Support:

ONGOING:

5P50MH090964 (Mann) NIMH 07/01/18 - 06/30/23
Conte Center: Antecedents of Suicidal Behavior Related Neurobiology
The Conte Center will employ a multidisciplinary approach to study how reported childhood adversity can mold the diathesis for suicidal behavior. These projects will help elucidate how early adverse experiences affect gene expression and brain biology to increase risk of suicidal behavior later in life.
Role on Project: PI

1R01EB026481 (PI: Zanderigo) 07/15/18 - 03/31/22
NIBIB
Noninvasive Quantification of Brain Glucose Metabolism Using a Portable Positron Emission Tomography Camera
New portable Positron Emission Tomography (PET) cameras with increased sensitivity over current PET scanners are paving the way for yet unexplored PET applications. However, a significant limitation in the use of portable PET devices, and PET imaging in general, is the need for continuous arterial blood sampling from the subject's arm during scan, for current gold-standard quantification of tracer uptake and binding to the target in relation to tracer blood levels. We will develop a new tissue- based, blood-free method to quantify the net influx rate of PET tracers with irreversible kinetics, validate the method using new collected [^{18}F]fluorodeoxyglucose data, and disseminate the software routines to allow use of this method for analysis of brain imaging data acquired with current and new generation PET scanners.
Role on Project: Co-Investigator

5R01MH109326 (Stanley, Oquendo) NIMH 05/15/16 - 02/28/21
Neurobiological Underpinnings of Two Suicidal Subtypes
The suicide rate continues to climb in the US. In 2013, the most recent year that statistics are available, the rate was the highest in over 25 years. This project will prospectively measure neurobiological, cognitive, and clinical risk factors and test a model showing 2 distinct subtypes of Suicidal Behavior (SB) through suicidal ideation that is either variable and reactive to stressors or sustained over time. Pharmacologic or psychological interventions targeting emotion regulation may be best for variable SI, while cognitive interventions may be better for sustained SI.
Role on Project: Co-Investigator

5R01MH108032 (Mann) NIMH 08/18/15 - 04/30/20
Familial Early-Onset Suicide Attempt Biomarkers
We seek to determine both resilience and vulnerability phenotypes for suicide attempts in major depressive disorder (MDD). Both phenotypes may aid estimation of risk and provide new targets for prevention intervention.
Role on Project: PI

5P01AG032959 (Kousteni) NIA 08/01/15 - 04/30/20

The Dialogue between Bone and the Brain: Endocrine and Molecular Bases:
Neuronal Control of Bone Mass by Sirt1
We have identified Sirt1 as a transcriptional regulator of the neuronal control of bone mass. In this application will test the hypothesis that one mechanism by which Sirt1 controls bone mass is by modulating sympathetic activity in the brain. The specific site of Sirt1 action in the brain and the molecular mechanisms through which Sirt1 modulate sympathetic tone will be investigated.
Role on Project: Collaborator

1R21MH112037 (Prabhakaran) NIMH 09/09/16 - 08/31/20 (NCE)
Development of GSK-3beta PET radioligands for in vivo imaging in brain
Glycogen kinase synthase-3 (GSK-3) has important role in psychiatric disorders and neurodegenerative diseases and are also targets for drug development. A specific GSK-3 positron emission tomography (PET) radiotracer can be a valuable tool for noninvasive imaging of the changes in GSK-3 in brain, thereby allowing accurate diagnosis, monitoring disease progression and accelerating the development of innovative medicines.
Role on Project: Co-Investigator

1R21DA041670-01A2 (Prabhakaran) NIDA 09/15/16 - 08/31/20 (NCE)
Evaluation of an [F-18] Agonist PET Ligand for 5HT2AR
Serotonin2A receptors (5HT2AR) have significant role in psychiatric disorders and neurodegenerative diseases and are also targets for drug development. A fluorine-18 labeled positron emission tomography (PET) radiotracer can be a commercially applicable tool for imaging changes in 5HT2AR in living brain, thereby allowing accurate diagnosis, monitoring disease progression and accelerating the development of innovative medicines.
Role on Project: Subaward Co-Investigator

5R01MH083862 (Boldrini) NIMH 05/23/14 - 04/30/20 (NCE)
Adult hippocampal neuroplasticity and depression
Major Depressive Disorder (MDD), one of the leading causes of global disease burden, is characterized by deficits in the anterior dentate gyrus (DG) of the hippocampus including reduced volume, granule neuron (GN) number and serotonin receptor (HTR) mRNA density. Conversely, serotonin reuptake inhibitor (SSRI), enhance DG proliferation, maturation, and survival, but the mechanism of action is unknown. We propose to elucidate this question with a unique approach combining human postmortem studies in well-characterized MDD, SSRI-treated MDD and controls, and studies in mice that are tissue-specific HTR knockouts or express engineered receptors, to test the hypothesis that SSRIs act, via HTRs, on intracellular cascades controlling hippocampal neuroplasticity, ultimately affecting behavioral responses to stress and antidepressant treatment.
Role on Project: Co-Investigator

<u>COMPLETED RESEARCH SUPPORT (within the past 3 years)</u>:

5P50MH090964 (Mann) NIMH 07/19/13 - 06/30/18
Conte Center: Antecedents of Suicidal Behavior Related Neurobiology
The Conte Center will employ a multidisciplinary approach to study how reported childhood adversity can mold the diathesis for suicidal behavior. These projects will help elucidate how early adverse experiences affect gene expression and brain biology to increase risk of suicidal behavior later in life.
Role on Project: PI

5R01MH096784 (Grunebaum) NIMH 07/05/12 - 07/31/18 (NCE)
Ketamine vs. Midazolam: Testing Rapid Relief of Suicide Risk in Depression
The primary goal is to test ketamine's potential anti-suicidal effects versus a similarly sedative control medication not known to reduce suicidal ideation. Exploratory aims include analysis of potential biological (salivary cortisol) and neuro-cognitive correlates as well as systematic assessment of suicidal ideation and behavior during continuation treatment.
Role on Project: Co-Investigator

DIG-0-163-12 (Mann) AFSP 10/01/13 - 10/01/18 (NCE)
Grieving Suicide: Clinical Aspects and Neural Circuitry

This study will help delineate the psychological components of grieving in family members of suicides. We will seek to determine the aspects of suicide related grief (SRG) that create a risk for further grief-related complications.
Role on Project: PI

4R01MH040210 (Underwood) NIMH 08/08/13 - 06/30/19 (NCE)
Postmortem Neurochemical Studies in Suicide
This study seeks to determine correlates of depression *versus* suicide at the level of source serotonergic neurons and target cortical elements. *We now have a group of* unmedicated major depression (MDD) nonsuicides to allow us to determine whether the changes we find are associated with *the diathesis of* suicide or with MDD. We propose a study of matched triplets (n=15) of an MDD suicide, an MDD nonsuicide and a nonpsychiatric nonsuicide control, all unmedicated and characterized psychiatrically. We aim to elucidate molecular mechanisms involved in regulating TPH2 expression and function in the dorsal raphe nucleus (DRN) and in the prefrontal cortex (PFC) and separate the effects of MDD from suicide. We hypothesize that the paradox of low 5-HT neurotransmission in the PFC and high TPH2 in the DRN in suicides is *a consequence of dysregulation of cAMP/PKA dependent and GSK3β pathways* regulating TPH2 phosphorylation *in the DRN* and signaling in the PFC. We predict that the serotonergic deficiency profile in suicide will be distinct from that in MDD.
Role on Project: Co-Investigator