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Biomarkers of Risk for Post-Traumatic Stress Disorder (PTSD)

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14. ABSTRACT The objective of this proposal is to study genetic and neuroendocrine biomarkers of risk in a carefully assessed population of military personnel who have recently returned from war zones. The target sample includes 300 men and women who have recently returned from hazardous deployment and are undergoing a comprehensive assessment of symptoms and stressors in a related 12-month longitudinal study. To date, we have enrolled 125 subjects. Samples of saliva have been obtained from all 125 enrolled subjects for analysis of DNA and candidate genes. Cortisol samples have been obtained from 96 of these subjects. Hormone and genetic data will be used to predict the development of PTSD and chronic PTSD. In addition, interactions of these biomarkers with trauma severity and other stressors as well as social supports will be examined.					
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Introduction

Experience from prior military conflicts and early data from Iraq and Afghanistan suggest that a significant percentage of troops on hazardous deployments will develop posttraumatic stress disorder (PTSD). This is one of the most common, debilitating, and chronic psychological disorders diagnosed among veterans. A large body of evidence in PTSD now documents dysfunction of the hormone system that coordinates the biological response to stress (the hypothalamic-pituitary-adrenal [HPA] axis). However, existing studies typically involve participants who have suffered from the disorder for many years, and information on biological processes occurring early in the disorder is lacking. In addition, specific genes that regulate HPA axis function have recently been identified in humans. Genes that are involved in the processing of emotions and cognition may also be involved in the pathogenesis of PTSD. In recent years investigators have begun to identify some of the relevant genes, and a few recent studies have identified specific gene-environment interactions that appear to confer risk for mood and anxiety disorders. The objective of this proposal is to study these biomarkers of risk in a carefully assessed population of military personnel who have recently returned from war zones. This study will enroll a target sample of 300 men and women who have recently returned from hazardous deployment in a war zone and are undergoing a comprehensive assessment of symptoms and stressors in a related 12-month longitudinal study. Samples of saliva will be obtained for analysis of DNA and candidate genes as well as hormone concentrations (cortisol). Hormone and genetic data will be used to predict the development of PTSD and chronic PTSD. In addition, interactions of trauma severity and other stressors as well as social supports with the biological factors will be examined. Findings of this study will contribute to knowledge about the biomarkers of risk for PTSD and will therefore increase our knowledge of the disease process and may help us to identify individuals who are at highest risk for PTSD.

Body

Task 1. To recruit subjects from a recently funded parent study of military personnel following warzone deployment who will provide biological specimens for hormone assay and genotyping for this study.

- a. Conduct screenings of potential participants who provided informed consent to the parent study
We consented 209 participants of the 238 who participated in the parent study.
- b. Collect biological specimens from participants
We collected 209 saliva samples for genetic analysis and 1600 cortisol samples from 160 individuals who were eligible and consented to participate in the neuroendocrine component of the study..

- c. Process and store biological specimens
All of the above genetic and cortisol specimens were catalogued and carefully processed.

Task 2. To assess neuroendocrine function and candidate genes and test these potential biomarkers for their association with the development and maintenance of PTSD.

- a. Hormone assays, University of Cincinnati, Dr. Thomas Geraciotti
All cortisol assays (1600 samples) were performed in duplicate and data received from Dr. Geraciotti's laboratory.
- b. DNA extraction and genotyping, VAMC Providence, Dr. John McGeary
Dr. McGeary's laboratory extracted DNA and genotyped 209 samples.
- c. Data management Butler Hospital, Dr. Audrey Tyrka
All biological data has been tracked, processed, sent for assay, results received and cleaned.
- d. Data analyses of initial assessment Butler Hospital, Dr. Audrey Tyrka
preliminary data analysis has been performed on the available baseline measures received from the parent grant. Follow-up measures have been collected recently and await data entry and analysis.

Cortisol data at baseline for 160 subjects are available presently for analysis. Additional cortisol samples were obtained at the 6-month follow-up because the present study was funded and began enrolling after the parent study began enrolling. Currently, only 11 participants who met the criteria for PTSD have cortisol data; these participants did not differ in their cortisol response to those who did not meet the PTSD criteria. Data regarding psychotropic medication use, comorbid diagnoses, and the longitudinal development of PTSD and chronic PTSD will be analyzed as data become available.

With the currently available cohort, repeated measures analysis of the effects of trauma exposure (Hoge scale) and childhood maltreatment (Childhood Trauma Questionnaire) on diurnal cortisol concentrations, controlling for effects of age, gender, and PTSD symptoms, showed a significant effect of trauma exposure over time ($F(4, 440) = 3.23, p=.003$) and a significant interaction of childhood maltreatment and combat trauma exposure over time ($F(4, 440) = 3.23, p=.01$). Among subjects with less combat trauma exposure, childhood maltreatment was associated with a decreased cortisol awakening response but no change in afternoon and evening cortisol concentrations. However, for those with greater trauma exposure, those with childhood maltreatment had blunted afternoon cortisol concentrations in comparison with participants who did not report childhood maltreatment. Chronic or prolonged trauma exposure has been linked with blunted cortisol concentrations in prior studies.

Preliminary data -genetics: We have extracted DNA samples from 209 participants and genotyped polymorphisms of the proposed candidate genes, including 5-HTTLPR, COMT s4680, DAT1 VNTR, as well as FKBP5, BDNF

val/met and NPY polymorphisms. Additional genes that will be genotyped include polymorphisms in the glucocorticoid receptor, the corticotropin-releasing hormone type 1 receptor, and angiotensin I converting enzyme (ACE).

Initial analyses of 18 participants who had trauma-related PTSD at the first assessment did not reveal any significant associations with these polymorphisms, or with genotype by trauma interactions. This may be due to insufficient power, and the lack of inclusion of subsequent diagnoses as well as lifetime diagnoses in these analyses. Further analyses will include past and follow-up PTSD diagnoses as the follow-up data are available for analysis. In addition, comorbidity will be examined with respect to outcome measure in relation to genetic and gene by environment effects.

Greater power was available for analyses of gene effects and gene by environment interaction effects on diurnal cortisol rhythms. In a model that assessed the effects of 5-HTTLPR x trauma exposure effects, controlling for age, sex, and PTSD symptoms, there was a significant interaction of 5-HTTLPR and childhood maltreatment ($F(4,114)=4.59, p=.002$). The effect of childhood abuse varied according to genotype. For subjects who were homozygous for the l allele, childhood maltreatment attenuated the cortisol awakening response and afternoon cortisol concentrations. But for those homozygous for the s allele, childhood maltreatment was associated with increased diurnal cortisol concentrations (heterozygotes were intermediate and those with childhood trauma did not differ from those without). Looking at this result from the alternate perspective, in the absence of childhood trauma, those with the LL genotype had increased diurnal cortisol concentrations, whereas for participants with childhood trauma, the l allele was linked to decreased cortisol awakening response and afternoon concentrations.

This finding is similar to an effect found for the COMT val/met polymorphism. After controlling for age, sex, and PTSD symptoms, there was an effect of COMT ($F(2,116)=7.75, p=.001$) and a COMT by childhood trauma interaction ($f(2,116)=6.59, p=.002$). Among participants who were homozygous for the Val allele, those with childhood maltreatment had increased diurnal cortisol concentrations, but among those homozygous for the Met allele, childhood maltreatment was associated with attenuated cortisol concentrations (and again, heterozygotes were intermediate and showed no effect of childhood trauma). Alternatively, in the absence of abuse, Val homozygotes had exaggerated cortisol concentrations, but among those with childhood abuse, Met homozygotes had exaggerated cortisol concentrations.

These findings suggest that genetic influences, as well as gene x environment interactions may underlie some of the mixed findings in the literature wherein cortisol is sometime attenuated in association with trauma, and in other studies is increased.

- e. Prepare manuscripts for publication Butler Hospital, Dr. Audrey Tyrka
Preliminary data analysis has begun as the data from the parent study have become available as discussed above. Further analysis and plan for manuscript preparation is underway.
- g. Data analyses of 12 month assessments (months 33-35) Butler Hospital, Dr. Audrey Tyrka
This data has not been analyzed because it is not yet available from the parent study.

- **Key Research Accomplishments**

- Total consented subjects: 209
- Total collected genetic samples: 209 subjects
- Total collected salivary cortisol: 160 subjects
- Processed and stored all specimens
- Conducted preliminary analyses with key findings described above.

Reportable Outcomes

Shea, MT, Tyrka, AR, Reddy, M, & Sevin, E. Psychosocial Risk Factors for PTSD in National Guard and Reserve Veterans Following War-Zone Deployment
Title of symposium: Marshall, E. C. & Vujanovic, A. A. (Chairs). (2010). *Trauma Exposure: Transdiagnostic Risk and Resilience Factors*. Symposium submitted for presentation at the 44th annual conference of the Association for Behavioral and Cognitive Therapies, San Francisco, CA.

Conclusion

These preliminary findings identify important genetic and environmental modifiers of diurnal cortisol rhythm in this sample of trauma-exposed combat veterans. Such alterations in stress hormone concentrations have been linked to changes in neurotransmitters and brain regions involved in depression and anxiety disorders including PTSD. Further analyses will aim to further elucidate the relationships between these biomarkers and the range of trauma experiences as well as protective factors such as social support on the development of PTSD.

(Title of symposium: Marshall, E. C. & Vujanovic, A. A. (Chairs). (2010). *Trauma Exposure: Transdiagnostic Risk and Resilience Factors*. Symposium submitted for presentation at the 44th annual conference of the Association for Behavioral and Cognitive Therapies, San Francisco, CA.)

Title: Psychosocial Risk Factors for PTSD in National Guard and Reserve Veterans Following War-Zone Deployment

Authors: M. Tracie Shea, Audrey Tyrka, Madhavi Reddy, & Elizabeth Sevin

The continuing return of veterans from wars in Iraq and Afghanistan increases the urgency of early identification of longer term problems. Despite increased knowledge of risk factors for PTSD (Brewin et al., 2000; Ozer et al., 2003), for military samples most research has been conducted many years after the trauma. Furthermore, meta-analysis has shown important difference between military and civilian samples in the relative importance of specific variables (Brewin et al., 2000). This presentation will report findings from a study designed to identify risk factors for PTSD symptoms and diagnosis in National Guard and Reserve veterans following deployment in Iraq or Afghanistan. The sample consists of 238 participants with post-deployment assessments, including structured interviews for PTSD (CAPS) and additional Axis I disorders (SCID-I), and a combination of interview and self report measures of hypothesized psychosocial risk factors. The latter includes pre-deployment variables (prior trauma, history of psychiatric disorder), deployment variables (severity of combat exposure, perceived threat, peritraumatic stress and dissociation, unit relationships and life / family concerns), and post-deployment variables (social support, life stressors, and negative affectivity). At the initial assessment, 24 (10.1%) of the sample met current criteria for PTSD. Findings from tests of hypothesized main, mediating, and moderating effects will be presented.

CURRICULUM VITAE
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EDUCATION

Undergraduate: State University of New York College at Purchase, Purchase, NY, B.A. Psychology,
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Pre-Medical: State University of New York College at Purchase, Purchase, NY, pre-medical
coursework, 1989-1991.

Columbia University, School of General Studies, New York, NY, Pre-Medical
Certificate, 1992

Medical School: University of Pennsylvania School of Medicine, Philadelphia, PA, M.D., 1999,
(combined M.D.-Ph.D. program, 1992-1999)

Graduate School: University of Pennsylvania, Department of Psychology, Philadelphia, PA, Ph.D.,
Psychology, 1999 (combined M.D.-Ph.D. program, 1992-1999)

PREDOCTORAL FELLOWSHIPS

1993-1994 Medical Scientist Training Program

1994-1999 NIMH National Research Service Award

POSTGRADUATE TRAINING

Residency: Resident in Psychiatry, Brown University School of Medicine, Providence, RI, 1999-
2003.

Research Track, Psychiatry Residency and the Mood Disorders Research Program and
Laboratory for Clinical Neuroscience, Butler Hospital and Brown University, 2001-2003.

PREDOCTORAL HONORS AND AWARDS

1988 B.A., Summa Cum Laude, State University of New York College at Purchase

1988 Award for Outstanding Undergraduate Research, State University of New York

1994 Robert M. Toll Psychiatry Research Prize, University of Pennsylvania

- 1999 AMA Rock Sleyster Memorial Scholarship
- 1999 Kenneth E. Appel Psychiatry Award, University of Pennsylvania School of Medicine

POSTGRADUATE HONORS AND AWARDS

- 2002 The American College of Psychiatrists 2002 Laughlin Fellowship Recipient.
- 2002 First Prize, Resident Research, Sixth Annual Research Symposium, Brown University School of Medicine Department of Psychiatry and Human Behavior
- 2003 American Psychiatric Association Research Colloquium for Junior Investigators, Participant and Travel Award Recipient
- 2003 NIMH Mentored Patient-Oriented Research Career Development Award
- 2003 Janssen Psychiatry Resident Award of Excellence
- 2003 NARSAD Young Investigator Award
- 2003 Janssen Pharmaceutica Faculty Development Award in Psychopharmacology
- 2003 NIH Clinical Research Loan Repayment Program
- 2004 American College of Neuropsychopharmacology Young Investigator Travel Award
- 2005 Future Leaders in Psychiatry Symposium Travel Award
- 2007 Outstanding Teaching Award in General Psychiatry, Warren Alpert Medical School of Brown University, Department of Psychiatry and Human Behavior
- 2009 The DBSA 2009 Gerald L. Klerman Young Investigator Award

PROFESSIONAL LICENSES AND BOARD CERTIFICATION

- Diplomate, National Board of Medical Examiners, 2000.
- Licensed Medical Doctor, Board of Medical Licensure and Discipline, State of Rhode Island and Providence Plantations, 2003.
- Diplomate, American Board of Psychiatry and Neurology, 2004.

ACADEMIC APPOINTMENTS

- Assistant Professor of Psychiatry and Human Behavior, Brown Medical School, Providence, RI, 7/03-
- Associate Chief, Mood Disorders Program, Butler Hospital, 7/03-

HOSPITAL APPOINTMENTS

Attending Psychiatrist, Butler Hospital, 2003-

Attending Psychiatrist, Kent County Memorial Hospital, Providence, RI 2003-

Assistant Unit Chief, General Treatment Unit Delmonico 4, Butler Hospital, 2005-2007

OTHER APPOINTMENTS

Editorial Board Member, Acta Psychiatrica Scandinavica, 2007-

Director, Trainee Editorial Board, Acta Psychiatrica Scandinavica, 2007-

Grant Reviewer, Special Emphasis Panel "NIMH Centers for Pediatric Mental Health." ZMH1-ERB-A-05, 6/07

Grant Reviewer, Special Emphasis Panel Department of Defense PTSD/TBI Post Traumatic Stress Disorder
Intramural #2, 11/07

Grant Reviewer, USAMRMC, Scientific Peer Advisory and Review Services, Panel on PTSD, 1/09

Grant Reviewer, USAMRMC, Scientific Peer Advisory and Review Services, Biomarkers of PTSD, 3/09

Grant Reviewer, USAMRMC, Scientific Peer Advisory and Review Services, Post-Traumatic Stress Disorder,
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Scientific Advisory Board Member, Depression Bipolar Support Alliance, 2010-

Ad Hoc Reviewer: American Journal of Psychiatry
Archives of General Psychiatry
Biological Psychiatry
Bipolar Disorders
Developmental Psychobiology
European Neuropsychopharmacology
Hormones and Behavior
Journal of Abnormal Psychology
Journal of Adolescent Health
Journal of Affective Disorders
Molecular Psychiatry
Neuropsychopharmacology
Pediatrics
PLoS ONE
Psychiatry Research
Psychological Medicine
Psychoneuroendocrinology
Psychopharmacology
Psychophysiology

HOSPITAL COMMITTEES

Butler Hospital Unit Leadership 2003-2006

Butler Hospital Physician's Subcommittee: Improvement of Organizational Performance 2004-

Butler Hospital President's Leadership Work Group 2007-

Butler Hospital Committee on Ethnic Diversity in Research Participation, 2006-2007

Butler Hospital Committee on Staff Wellness Programs 2008-2009

UNIVERSITY COMMITTEES

Brown Medical School: Medical Curriculum Committee, Subcommittee on Years 3 and 4, 2004-6

MEMBERSHIPS IN SOCIETIES

American Psychiatric Association 1989-

Rhode Island Psychiatric Society, 2004-

Society of Biological Psychiatry, 2005-

American College of Neuropsychopharmacology Associate Member, 2007-

ORIGINAL PUBLICATIONS IN PEER-REVIEWED JOURNALS

1. **Tyrka, A.** and Smith, G.P. Potency of SCH 23390 for decreasing sucrose intake in rat pups depends on mode of ingestion. Pharmacology Biochemistry & Behavior, 39(4):955-961, 1991.
2. Smith, G.P., **Tyrka, A.** and Gibbs, J. Type-A CCK receptors mediate the inhibition of food intake and activity by CCK-8 in 9- to 12-day-old rat pups. Pharmacology Biochemistry & Behavior, 38(1):207-210, 1991.
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4. **Tyrka, A.**, Gayle, C. and Smith, G. P. Raclopride decreases sucrose intake of rat pups in independent ingestion tests. Pharmacology Biochemistry & Behavior, 43(3):863-869, 1992.
5. Miesner, J., Smith, G. P., Gibbs, J., and **Tyrka, A.** Intravenous infusion of CCK-A receptor antagonist increases food intake in rats. American Journal of Physiology, 262(2):R216-R219, 1992.
6. **Tyrka, A.** and Smith, G. P. SCH 23390, but not raclopride, decreases intake of intraorally

infused 10% sucrose in adult rats. Pharmacology Biochemistry & Behavior, 45(1):243-246,1993.

7. **Tyrka, A.R.**, Cannon, T. D., Haslam, N., Mednick, S.A., Schulsinger, F., and Schulsinger, H. The Latent Structure of Schizotypy I: Premorbid indicators of a taxon of individuals at-risk for schizophrenia spectrum disorders. Journal of Abnormal Psychology, 104: 173-183, 1995.
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10. Graber, J.A., **Tyrka, A.R.**, and Brooks-Gunn, J. How similar are different subclinical eating problems and bulimia nervosa? Journal of Child Psychology and Psychiatry, 44 (2) 262-273, 2003.
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12. Carpenter, L.L., **Tyrka, A.R.**, McDougle, C.J., Malison, R.T., Owens, M.J., Nemeroff, C.B., and Price, L.H. Cerebrospinal fluid corticotropin releasing factor and perceived early life stress in depressed patients and healthy control subjects. Neuropsychopharmacology, 29 (4) 777-784, 2004.
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14. Carpenter, L.L., Schechter, J.M., Underwood, J.A., **Tyrka, A.R.**, and Price, L.H. Service expectations and clinical characteristics of patients receiving psychiatric emergency services. Psychiatric Services, 56: 743-745, 2005.
15. Carpenter, L.L., Milosavljevic, N., Schechter, J.M., **Tyrka, A.R.**, and Price, L.H. Augmentation with open-label atomoxetine for partial or nonresponse to antidepressants. Journal of Clinical Psychiatry, 66, 1234-8, 2005.
16. Carpenter, L.L., Schechter, J.M., **Tyrka, A.R.**, Feijo de Mello, A., Feijo de Mello M., Haggarty, R., and Price, L.H. Open-Label Tiagabine monotherapy for major depressive disorder with anxiety. Journal of Clinical Psychiatry, 67, 66-71, 2006.
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29. Philip, N.S., Carpenter, L.L., **Tyrka, A.R.**, and Price, L.H. Augmentation of antidepressants with atypical antipsychotics: A review of the current literature. Journal of Psychiatric Practice, 14, 34-44, 2008.

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31. **Tyrka, A.R.**, Wier, L.M., Price, L.H., Ross, N.S., and Carpenter, L.L. Childhood parental loss and adult psychopathology: Effects of loss characteristics and contextual factors. *International Journal of Psychiatry in Medicine*, 38(3), 329-344, 2008.
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- A74. **Tyrka, A.R.**, Price, L.H., Walters, C., Anderson, G.M., and Carpenter, L.L. Hypothalamic-Pituitary-Adrenal Axis Activity and Indices of the Metabolic Syndrome. Annual Meeting of the American College of Neuropsychopharmacology, December, 2009.
- A76. Carpenter, LL, **Tyrka, AR**, Geraciotti, TD, Shattuck, TT, and Price, LH. Diminished Cortisol Response to Stress in Healthy Adults Reporting Physical Abuse. Annual Meeting of the American College of Neuropsychopharmacology, December, 2009.
- A77. Shea, MT, Tyrka, AR, Reddy, M, and Sevin, E. Psychosocial Risk Factors for PTSD in National Guard and Reserve Veterans Following War-Zone Deployment. Symposium submitted for presentation at the 44th annual conference of the Association for Behavioral and Cognitive Therapies, San Francisco, CA.)

INVITED PRESENTATIONS

1. "Psychotic Depression." Butler Hospital Case Conference Series, 2/26/04, Regional Presentation.
2. "New Views on Women and Depression." Women and Infants Hospital Annual Women's Health Conference, 1/15/05, Regional Presentation.
3. "Risk for Depression: It's Nature *and* Nurture." Academic Meeting of the Butler Hospital Board of Trustees, 3/22/05, Regional Presentation.
4. "Sensitivity to Stress and Risk for Depression." Academic Presentation to the Butler Hospital Staff Association, 4/7/05, Regional Presentation.

5. "Clinical Psychiatry: Diagnosis and Management." Lecturer for Falcon Reviews, 6/05-5/06, National Presentation.
6. "Trauma and Psychopathology: Psychosocial and Biological Factors Influencing Risk and Resilience." Second Annual Joint Conference Butler Hospital and Family Service of Rhode Island, 3/24/06, Regional Presentation.
7. "Risk for Major Depression: Genes, Stress, and the HPA Axis," American Psychiatric Association 159th Annual Meeting, Toronto, May, 2006, National Presentation.
8. "Current Research and Significance of Childhood Trauma: Effects on Adulthood" . Women and Infants Hospital Annual Women's Health Conference, 5/15/07, Regional Presentation.
9. "Stress Sensitivity and Risk for Psychopathology: Genes, Experience and HPA Axis Function." Distinguished Faculty Speaker, Twelfth Annual Brown University Research Symposium, March, 2008, Regional Presentation.
10. "Corticotropin releasing hormone receptor (CRHR1) polymorphisms interact with early life stress to influence the cortisol response to the Dex/CRH test: Preliminary findings." Paper presented at the Annual Meeting of the Society of Biological Psychiatry, May, 2008, National Presentation.
11. "Neurobiology of Anxious Depression." American Psychiatric Association 162nd Annual Meeting, San Francisco, May 2009, National Presentation
12. "Depression and Bipolar Disorder: Ask the Doctor Panel" Depression and Bipolar Support Alliance National Conference, September, 2009, National Presentation
13. "Alternative Treatments: Evaluating Your Options" Depression and Bipolar Support Alliance National Conference, September, 2009, National Presentation

GRANTS

1. 5 F30 MH10819-03 Predoctoral National Research Service Award, "Neuropsychological Indicators of Risk for Schizophrenia," Principal Investigator, 9/94-5/00.
2. NARSAD (Young Investigator Award), "Hypothalamic-Pituitary-Adrenal Function in Adults with a History of Early Life Stress," Principal Investigator; 6/03-5/05,
3. Janssen Pharmaceutica Faculty Development Award in Psychopharmacology, 5/18/03, \$25,000.
4. RSGPB PBP-103382 American Cancer Society, "Improving Smoking Cessation in Smokers with Depressive Symptoms", role: study physician, 7/02-6/04
5. Medtronic, Inc., "Electrical Stimulation of the Anterior Limb of the Internal Capsule to Treat Major Depressive Disorder," Co-Investigator, 10/02-9/04,

6. 1K23MH067947-1A1 Mentored Patient-Oriented Research Career Development Award, “Risk for Depression, Stress, and Neuroendocrine Function,” Principal Investigator; 12/03-11/08, .
7. Pfizer, Inc. “Sertraline Treatment and Cortisol Response to the DEX/CRH Test”, Investigator-Initiated, Co-Investigator, 1/04-11/06,
8. United States Department of the Interior, “Perceived Early Life Stress and DEX/CRH Test Response as Predictors of Psychological Sequelae following Exposure of Healthy Adults to War Stress,” Co-Investigator, 7/04-6/05,
9. UCB Pharma, Inc. “Keppra Treatment and Cortisol Response to the DEX/CRH Test in Healthy Subjects,” Investigator-Initiated, Co-Investigator, 6/04-5/07,
10. NCCAM/NIMH AT001742-01, "Double-blind, placebo-controlled study of SAME vs. escitalopram in MDD," Co-Investigator, 4/04 - 3/09,
11. United States Department of Defense, “Biomarkers of risk for post-traumatic stress disorder (PTSD),” Principal Investigator, 4/07-4/10,
12. Cyberonics, Inc. “Randomized Comparison of Outcomes in Patients with Treatment-Resistant Depression Who Receive VNS Therapy Administered at Different Amounts of Electrical Charge” Co-Investig; 11/1/07-present; \$
13. Medtronic, Inc. “RECLAIM Deep Brain Stimulation (DBS) Clinical Study for Treatment- Resistant Depression.” Multi-Site; Co-Investigator 4/16/2009-
14. R01 MH0687670-01 “DEX/CRH Response: Mood/Anxiety Disorder Endophenotype? Phase 2.” Co-Investigator, 12/08-11/13, .
15. R01 MH083704-01 “Childhood Maltreatment: Biomarkers of Risk and Resilience.” Principal Investigator, 12/09-11/14,

UNIVERSITY TEACHING ROLES

Psychiatric Interviewing, PGY 1 Residents, 2003-present.

Introduction to Psychiatric Literature, PGY 1 Residents, 2003-2004

Mood Disorders Psychopharmacology lectures, PGY 1-4 Residents, 2003-present.

Mood Disorders Psychopathology lectures, PGY 1-4 Residents 2003-present .

Grant Reviewer, Post-doctoral fellows grantsmanship workshop 2004-2006

Research Supervisor, Post-Doctoral Psychology Fellows 2004-2007

Dissertation Committee Member, Pre-Doctoral Psychology Student 2005-2007

Course Director/Instructor, Principles of Biostatistics, T32 Post-Doctoral Fellows, 2006-2008

Morbidity and Mortality Conference Preceptor, PGY 1-4, 2007

Supervisor, Brown University Psychology Department senior student Independent Research Project 2007-2008

Supervisor, Brown University Neuroscience Concentrator senior student Independent Research Project 2008-2009

HOSPITAL TEACHING ROLES

Supervisor/preceptor, 3rd- and 4th-year Brown medical student clerks, 2003-2007

Supervisor, Brown psychiatry residents (Inpatient; PGY-1 - PGY-4), 2003-2007

Doctor-on-call supervisor, Butler Hosp. Patient Assessment Service, 2003-present.

Supervisor, Brown psychiatry residents (Outpatient, PG-3), 2003-present.