Award Number:
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TITLE:
Biomarkers of Risk for Post-traumatic Stress Disorder (PTSD)

PRINCIPAL INVESTIGATOR:
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CONTRACTING ORGANIZATION:
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The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.
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 203 subjects. Samples of saliva have been obtained from all 203 enrolled subjects for analysis of DNA and candidate genes. Cortisol samples have been obtained from 157 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.
# Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>1</td>
</tr>
<tr>
<td>Body</td>
<td>1</td>
</tr>
<tr>
<td>Key Research Accomplishments</td>
<td>1</td>
</tr>
<tr>
<td>Reportable Outcomes</td>
<td>2</td>
</tr>
<tr>
<td>Conclusion</td>
<td>3</td>
</tr>
<tr>
<td>References</td>
<td>3</td>
</tr>
<tr>
<td>Appendices</td>
<td>4-21</td>
</tr>
</tbody>
</table>
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

This year we consented 78 subjects who were eligible for the study and collected genetics samples on all of them. We received salivary cortisol back from 61 subjects this year. All specimens have been catalogued, processed, and stored. All collection materials have been ordered. We renewed our IRB approval. We started running assays and analyses will be done in year of the grant.

Key Research Accomplishments

- Total consented subjects: 203
- Total collected genetic samples: 203 subjects
- Total collected salivary cortisol: 157 subjects
- Processed and stored all specimens
• Started to run assays and do preliminary analyses
• Started to clean data
• Renewed IRB approval

Reportable Outcomes

The data presented below reflect preliminary analyses with the available data.

**Cortisol:** Cortisol data for 93 subjects are available presently for analysis. A repeated measures analysis of the effects of trauma exposure (Hoge scale) and current PTSD symptoms, controlling for effects of age, showed a significant effect of PTSD symptoms over time \(F(4, 85) = 2.95, p = .025\) and a significant interaction of PTSD symptoms and trauma exposure over time \(F(4, 85) = 6.85, p < .001\). As shown in the figure to the right, among subjects with moderate trauma exposure (Hoge score at or above the median of 10), those with PTSD symptoms had higher cortisol concentrations upon awakening and 30-minutes following awakening.

**Genetics:** Preliminary data -genetics: We have extracted DNA samples from the first 148 samples and genotyped them for the 5HTTLPR (trallelic data), COMT rs4680 SNP and, DAT VNTR. Genotype frequencies were SS: \(n = 33 (22.3\%)\), SLG: \(n = 0 (0\%)\), LGLG: \(n = 0 (0\%)\), SLA: \(n = 74 (50\%)\), LGLA: \(n = 9 (6.1\%)\), and LALA: \(n = 32 (21.6\%)\). COMT rs4680 genotype frequencies were: Met/Met: \(n = 37 (32\%)\), Val/Met: \(n = 51 (44.7\%)\), Val/Val: \(n = 26 (23\%)\). DAT VNTR genotype frequencies were: 9/9: \(n = 10 (6.7\%)\), 10/9: \(n = 60 (40.5\%)\), 10/10: \(n = 78 (52.7\%)\). Initial analyses did not reveal any significant associations between genotype and PTSD diagnosis. This may be due to insufficient power, so the next steps will be to genotype additional samples. Further analyses will examine the importance of comorbid diagnoses, degree of trauma exposure, and will include potentially critical covariates such as childhood maltreatment.
Conclusion

Recruitment and collection of genetic and salivary cortisol specimens has been proceeding according to timeline. We have started to run assays, clean data and will run final analysis in year3.

References

N/A

Appendix

Dr. Tyrka’s CV is attached.

Supporting Data

N/A
CURRICULUM VITAE
AUDREY R. TYRKA, M.D., PH.D.

Business Address: Butler Hospital, Brown Medical School Department of Psychiatry and Human Behavior, 345 Blackstone Blvd, Providence, RI 02906
Business Tel: (401) 455-6520
Business Fax: (401) 455-6534
E-mail: Audrey_Tyrka@Brown.edu

EDUCATION


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)


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

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.

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
Grant Reviewer, Special Emphasis Panel Department of Defense PTSD/TBI Post Traumatic Stress Disorder Intramural #2
Ad Hoc Reviewer: American Journal of Psychiatry
Archives of General Psychiatry
Biological Psychiatry
Bipolar Disorders
Developmental Psychobiology
European Neuropsychopharmacology
Journal of Abnormal Psychology
Journal of Adolescent Health
Journal of Affective Disorders
Molecular Psychiatry
Neuropsychopharmacology
Pediatrics
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-

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


**OTHER PEER_REVIEWED PUBLICATIONS**


**BOOKS AND BOOK CHAPTERS**


**OTHER NON_PEER_REVIEWED PUBLICATIONS**


**PUBLICATIONS IN PREPARATION**


**ABSTRACTS**


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.


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.


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.


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, $60,000.

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


6. 1K23MH067947-1A1 Mentored Patient-Oriented Research Career Development Award, “Risk for Depression, Stress, and Neuroendocrine Function,” Principal Investigator; 12/03-11/08, $905,000.


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, $40,000


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; $230,000.


15. R01 MH086555-01 “Biomarkers of Risk and Resilience to Adversity.” Principal Investigator, 7/01/09-6/30/14, pending,
16. R01 MH085838-01 “Onset and maintenance of PTSD in Iraq Veterans: a longitudinal study of psychosocial and biological risk factors.” Co-Principal Investigator, 12/01/09-11/01/14 pending, 3,907,421

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


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


HOSPITAL TEACHING ROLES


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


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