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The Root Cause of Post-traumatic and Developmental Stress Disorder

PRINCIPAL INVESTIGATOR:
Keith A. Young, PhD

CONTRACTING ORGANIZATION:
Texas A&M Health Science Center
Temple Texas 76504

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14. ABSTRACT

Our overarching scientific hypothesis holds that serotonergic influences on brain development driven by genetics and early experience induce a variation of normal brain anatomy that makes the brain highly susceptible to the effects of severe stress. We are studying this question using both clinical and basic approaches. New findings from our lab funded by VA support the existence of an anatomical phenotype conferring susceptibility to depression, and the current work seeks to extend these findings to PTSD. Project 2 (Fluoxetine in active duty troops) has begun to enroll subjects at Fort Hood and will provide genetic material for this project. To allow use of new VA MRI VA research facilties, and to improve design, power and military application, a revised change in scope to project 5 has been submitted to allow all the work to be performed in OEF/OIF veterans. In the cellular level anatomical study, 15 brains have been identified and tissue processing is being initiated. The animal project work is approximately ½ finished and task 2 is being initiated.

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No subject terms provided.

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INTRODUCTION:

Our overarching scientific hypothesis holds that serotonergic influences on brain development driven by genetics and early experience induce a variation of normal brain anatomy that makes the brain highly susceptible to the effects of severe stress. The goal of Project 1 is to describe the progression of post-deployment stress disorders (PTSD, major depression, suicidality) in active duty troops, and to investigate developmental and environmental factors that influence predisposition to PTSD and depression. In coordination with this effort, we have begun patient recruitment on a therapeutic trial of the serotonin reuptake inhibitor fluoxetine, to determine whether it can alter the trajectory of post-deployment PTSD (Project 2: This proposal is funded by CDMRP). Using DNA gathered from Projects 1 and 2 (and 5), Project 3 will investigate genetic factors influencing resiliency and susceptibility to stress disorders and therapeutic response to fluoxetine. Projects 4 and 5 are designed to elucidate basic relationships between genetic variation in the serotonin system, limbic brain anatomy, brain function and behavior. Project 4 will investigate post-mortem anatomy in subjects with major depression, while Project 5 will investigate anatomical and functional brain changes in subjects exposed to varying levels of chronic and traumatic stress. Finally, animal models (Project 6) are being used to investigate the development of the brain anatomical stress susceptibility phenotype and to screen for novel agents with potential to treat PTSD and depression. An overarching goal of the Program is integration of data across the projects to compare and contrast the potential for different assessment paradigms (MRI anatomy, fMRI, evoked potentials, startle, genetic profiling) to screen for resiliency and predisposition to post-traumatic and developmental stress disorder stress disorders.

BODY:

KEY RESEARCH ACCOMPLISHMENTS:

Administrative:

Using partial funding available as of date, equipment purchases, setup, procedure validation and work on initial projects was performed in 2009/10. Also during this period of time, the VA research dedicated mobile 3T MRI (which will be used in revised Project 5) was completed and testing pads built at Waco, Temple and Fort Hood. This equipment is now ready to service the CDMRP project. In year 3 (2008-2009), HSRRB review was completed for "Fluoxetine treatment of active duty troops" and enrollment is underway at Fort Hood. Submission of a DNA consent for this protocol is under review at this time, to allow existing specimens from the Fluoxetine study to be used for additional genetic studies (BAMC IRB). In Spring 2009, local IRB approval for the initial MRI study was obtained from the VA. Revisions and rebudgeting of the protocol to incorporate the CDMRP final funding and to allow use of the new VA mobile unit have been submitted, and based on forthcoming recommendations, the VA IRB will be forwarded for HSRRB approval. Additional MOUs with Darnall to provide space for recruitment at Fort Hood is in revision.

Project Specific:

Task 1: Sample 1400 active duty/guard troops
a. Diagnostic interview (MINI)
b. CAPS/depression symptoms
c. Stress battery (DRRI, development history, suicidality)
d. DNA, cortisol
e. RBANS (cognitive screen)
Task 2: Resample/test at ~ 4 - 6 mo
Task 3: Follow-up contact at 1 year for pathways to mental health care.
1a Deliverable: Progression of stress disorder in post-deployment troops
1b Deliverable: Multiple genetic and psychosocial factors alter the trajectory of military PTSD
2a Deliverable: Postdeployment pathways to mental healthcare

Progress 03/29/10

Awaiting IRB approval

Project 2 Fluoxetine for post-deployment stress disorder

Task 1: Fluoxetine/placebo supplementation of standard of care in active duty troops (mo 5- 40)
Task 2: Open label fluoxetine extension
Task 3: Exploratory analysis of factors contributing to fluoxetine response

Progress 03/29/10

Subject recruitment has been initiated. Collection of DNA in progress

Project 3 Serotonin and other genes and biomarkers

Task 1: Compare biologic factors: susceptible vs. resilient (Project 1) and treatment responsive vs. non-responsive (Project 2)
a. SERT-ss vs. SERT-sl/ll
b. Biomarkers
3a Deliverable: Salivary cortisol levels predict response to traumatic stress
Task 2: Serotonin and additional genes
3b Deliverable: Serotonin pathway gene alleles contribute to 5HTTLPR effects on PTSD
Task 3: Multi-locus analysis
3c Deliverable: Factors affecting fluoxetine response in treatment of PTSD symptoms

Progress 03/29/10

Collection of DNA in progress (see above)/lab genetic methods are being validated

Project 4 Serotonin and other genetic effects on cellular level brain anatomy.

Task 1. Compare regional volumes and neuronal populations in SERT-ss vs. sl/ll

4a Deliverable: 5HTTLPR effects on the thalamic/cingulate ratio.

Task 2. Compare serotonin fiber density in SERT-ss vs. SERT-sl/ll thalamus

4b Deliverable: 5HTTLPR effects on thalamic and cingulate serotonin fiber density.

Progress 03/29/10

15 brains have been identified and histological procedures are being initiated (Spring 2010).

Project 5 Serotonin and other genetic effects on regional brain anatomy and function (revised aims 03/29/10)

This project was originally designed to scan 200 subjects (160 community volunteers, 20 resilient and 20 PTSD) and perform psychophysiological testing-only in additional 100. Availability of research scanner at CTVHCS/Fort Hood makes it possible to scan 300 subjects at Fort Hood and CTVHCS and perform psychophysiological testing in all 300 subjects.

Task 1: Compare thalamic anatomy and startle/evoked potentials in controls and PTSD with SERT as a cofactor.

5a Deliverable: Thalamic enlargement and startle in PTSD.

5b Deliverable: 5HTTLPR short allele is associated with thalamic enlargement and potentiated baseline startle.

Task 2: Compare effect of emotional probes on startle/evoked potentials in normal controls and PTSD

5c Deliverable: Facial fear effects on startle and evoked potentials are potentiated in subjects with the 5HTTLPR short allele.

Progress 03/29/10

All VA MRI and psychophysiological equipment needed to perform the proposed work has been installed and tested in VA protocols. Initial data from these VA protocols confirms the presence of a brain anatomical phenotype related to serotonin genetic variation and susceptibility to depression, consisting of thalamic enlargement and related anatomical changes. A manuscript describing these findings is being prepared. CDMRP funding will be used to extend this finding to PTSD. The above proposed revised aims will consolidate the original 3 separate cohorts (N=40, N=260, N=100) into a single OEF/OIF cohort to improve design, power and military applications.

Project 6 Anatomical and behavioral animal models of developmental stress disorders

Task 1: Develop relevant rodent models

a. Developmental environmental effects on thalamic/cingulate anatomy, behavior and electrophysiology

a1. Prenatal stress

6a Deliverable: Prenatal stress reduces the cingulate/thalamic volume ratio and potentiates adult depressive and aggressive behavior.

a2. Postnatal stress

6b Deliverable: Early post-natal stress reduces the cingulate/thalamic volume ratio and potentiates adult depressive and aggressive behavior

b. Developmental serotonergic effects on thalamic/cingulate anatomy, behavior and electrophysiology

6c Deliverable: Prenatal elevation of serotonin levels reduces the cingulate/thalamic volume ratio and potentiates adult depressive and aggressive behavior

Task 2: Use rodent model(s) as screens

a. Effect of the anatomical brain stress phenotype on ETOH intake

6d Deliverable: Prenatal stress accentuates ETOH intake and reduces adversive effects of high dose ETOH

b. Preclinical testing for PTSD agents

6e Deliverable: Effect of peritraumatic and adult administration of fluoxetine on development of long-term behavioral patterns in rats

Progress 03/29/10

Analysis of Task 1 suggested that post-natal stress was the most effective intervention in altering thalamic anatomy. Task 2 is being initiated based on the results of the study.

REPORTABLE OUTCOMES: None

CONCLUSION: No scientific conclusions have been made at this point in time.

APPENDICES: None.