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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. Animal studies have been completed and the tissue is now being analyzed. Post-mortem brain tissue from 6 of the brains collected are being used for a transcriptome study to investigate RNA expression in two areas of the cortex. In 2011, the project was transferred to TATRC for management. As required when they take over management of a project, TATRC convened a review panel that recommended revisions in the goals of the project. The suggestions were accepted and the clinical portion of the project will be redesigned in the remainder of 2011 to involve a pre-deployment/post-deployment longitudinal study with a subset receiving MRI assessments, rather than the previous design (post-deployment only). The revised budget will be resubmitted in July and the new project will be initiated next fall, after IRB and HRPO review.					
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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 new goal of Project 1 is to describe the progression of post-deployment stress disorders (PTSD, major depression, suicidality) in active duty troops using predeployment/postdeployment structured clinical interviews, and to investigate developmental and environmental factors that influence predisposition to PTSD and depression. A subset of participants will be selected to have predeployment/postdeployment MRI analysis. 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 clinical trials, Project 3 will investigate genetic factors influencing resiliency and susceptibility to stress disorders and therapeutic response to fluoxetine. A panel of 15 genes has been tested and validated. Projects 4 and 5 were designed to elucidate basic relationships between genetic variation in the serotonin system, limbic brain anatomy, brain function and behavior. Project 4 is investigating post-mortem anatomy in subjects with major depression and PTSD, while Project 5 is investigating 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. The revised program has been designed maintain this overarching goal.

BODY:

KEY RESEARCH ACCOMPLISHMENTS:

Administrative:

Final funding for the program was received and is being budgeted in 2011. Equipment purchases, setup, procedure validation and TATRC-suggested redesign was performed in 2010/11. Redesign of the overall budget will be completed by September 30, 2011. The redesigned Project 1 will be submitted for review by BAMC and HRPO in 2011.

Project Specific: Redesigned

Task 1: Sample 4000 active duty/guard troops predeployment

- a. Diagnostic interview (MINI/SCID)
- b. CAPS/depression symptoms
- c. Stress battery (DRRI, development history, suicidality)
- d. DNA, cortisol
- e. Medical testing (CBC/TSH/CMP)

Task 2: Resample/test post-deployment

Progress 03/29/11

Redesigned by recommendation of TATRC review process

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.

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

Task 2: Serotonin and additional genes

Task 3: Multi-locus analysis

Progress 03/29/11

Panel of 15 genes validated and tested.

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

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

Progress 03/29/11

22 brains have been identified and a test brain has been sectioned and processed. A subset of PTSD tissue is being prepared for transcriptome (RNA expression) analysis of BA 45 and 9 in 2011.

Project 5 Serotonin and other genetic effects on regional brain anatomy and function.

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

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

Progress 03/29/11

As previously approved, the VA portion of this experiment was approved by VA IRB and submitted to HRPO for pre-review in 2010. However, the redesign of the program does not include a VA MRI component. The redesigned MRI component will be resubmitted to BAMC and HRPO in 2011.

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
 - a2. Postnatal stress
- b. Developmental serotonergic effects on thalamic/cingulate anatomy, behavior and electrophysiology

Task 2: Use rodent model(s) as screens

- a. Effect of the anatomical brain stress phenotype on ETOH intake
- b. Preclinical testing for PTSD agents

Progress 03/29/11

Animal studies have been completed and tissue analysis is in process.

REPORTABLE OUTCOMES: None

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

APPENDICES: None.