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The Root Cause of Post-traumatic and Developmental Stress Disorder

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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. In year 1, equipment purchases, setup and initial IRB submissions were initiated. In year 2, local IRB approvals for 3 projects have been completed and we are awaiting HSRRB review on these projects (1. Fluoxetine treatment of active duty troops, 2. Genetic influences on emotional processing and brain structure: Longitudinal stability and variability, 3. The root cause of post-traumatic and developmental stress disorder: Reflex responses to facial emotion). An additional funding supplement and a change in scope to project 5, which will extend the MRI patient recruitment to include active duty troops at Fort Hood using a newly acquired mobile 3T MRI (provided by the VA) was implemented in FY2007-2008. A new subcontract with UTHSCSA was approved to provide existing brain material. Animal project work is approximately ½ finished. Behavioral analysis indicates that both pre- and post-natal isolation stress alters the behavior of adult animals. Histological and stereological work on the brains from these animals is now in progress to complete these tasks.

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Table of Contents

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 will implement 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. An additional supplement to project 5, which will extend the MRI patient recruitment to include active duty troops at Fort Hood using a newly acquired mobile 3T MRI received in FY2007-2008, and we are awaiting HSRRB review to DOD funding for this project. 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:

Full funding of the main contract and subcontracts was completed in August of 2007, and equipment purchases and setup was completed in 2008. In year 2 (2007-2008), local IRB approvals for parts of 3 projects have been completed and we are awaiting HSRRB review completion (1. Fluoxetine treatment of active duty troops, 2. Genetic influences on emotional processing and brain structure: Longitudinal stability and variability, 3. The root cause of post-traumatic and developmental stress disorder: Reflex responses to facial emotion). There is no separate IRB for project 4 (DNA analysis), rather, each project incorporates the procedures in the existing 3 IRBs. An additional funding supplement and a change in scope to project 5, which will extend the MRI patient recruitment to include active duty troops at Fort Hood using a newly acquired mobile 3T MRI (provided by the VA) was approved and funded in March, 2009. At the same time, a subcontract with UTHSCSA was approved to provide existing brain material. An MOU allowing access of the mMRI to Darnall has been approved, And an additional MOU with Darnall to provide space for recruitment is now under Review.

Project Specific:

Project 1 Early progression of post-deployment stress disorders (phase 1: post-deployment)

Task 1: Sample 1400 active duty/guard troops < 6 wks post-deployment

a. CAPS/depression symptoms
b. Stress battery (DRRI, development history, suicidality)
c. DNA, cortisol
d. RBANS (cognitive screen)

Task 2: Resample/test at ~ 6mo

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 03/24/09

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

No deliverables: funded by PDMRP (awaiting HSRRB approval)

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: SERT-ss genotype predicts 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 03/24/09

Awaiting HSRRB approval

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 03/24/09

Subcontract to acquire the brains from UTHSCSA is being negotiated.

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.

5a Deliverable: Thalamic enlargement and startle in PTSD.

5b1 Deliverable: 5HTTLPR short allele is associated with thalamic enlargement and potentiated baseline startle.

5b2 : Thalamic enlargement and startle in PTSD in active duty troops

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 03/24/09

Equipment to obtain psychophysiological data has been approved by local IRBs and we are awaiting HSSRD approval for funding of this portion of the project. Equipment to perform new aim # 5b2 (MRI assessment in active duty troops) has been set-up and is being tested. The mobile 3T MRI from Phillips (funded by the VA) was received in July with COL Phillips from Fort Hood attending. The pad site for the MRI (funded by the VA) at Fort Hood was completed in 2008 allowing imaging work to be performed in active duty troops. A change in scope to perform this additional work as part of project 5 has been approved by MOMRP. Research equipment was installed and the machine was handed over to the VA in February, 2009. An MOU allowing access of the machine to Darnall has been approved and the unit will be moved to Darnal for testing early this summer. In 2007-2008, using existing, de-identified 3T MRI data from a previous project, we compared thalamic manual outlining procedures to automated segmentation routines (Primarily Freesurfer). The automated procedures were very inaccurate at identifying the ventrolateral borders of the thalamus, and resulted in considerably more variability in thalamic volumes than the manual procedures. In 2009, we developed a new procedure for automatic segmentation using FSL that was very accurate (r2=0.89. We will use this automated procedure in our analysis for project 5. A manuscript using this analysis is in preparation.

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 03/24/09

*Animals in Task 1 have all been completed, and the brains are being analyzed. Currently, deliverable 6a and 6b (prenatal and post-natal stress models) are fully completed. Behavioral testing has been completed and the brains are being prepared for histology and stereology. Initial analysis of behavior alone suggests that the early developmental interventions altered behavior. We will complete the histological analysis before proceeding to 6c and Task 2. An abstract at the Society for Neuroscience about the behavioral data from the study was presented in 2008 (*L. J. Miller, R. M. Kressin, N. B. Keele, K. A. Young The role of early life stress on fear learning and depression-like behavior in rats. Soc. Neurosci. Ann. Mtg. 2008; 820.14).

REPORTABLE OUTCOMES: None
CONCLUSION: No scientific conclusions have been made at this point in time.
APPENDICES: None.