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TITLE: Basic Cognitive Neuroscience of Memory and Self-Appraisals in PTSD

PRINCIPAL INVESTIGATOR: Charles R. Marmar, MD

CONTRACTING ORGANIZATION: New York University (INC)
New York, NY 10016-6402

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Charles R. Marmar, MD

E-Mail: Charles.Marmar@nyumc.org

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550 1st Avenue
New York, NY 10016-6402

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14. ABSTRACT
This proposal seeks to employ theories and paradigms from cognitive neuroscience to identify cognitive and neurobiological mechanisms underlying the relation between changes in self-efficacy (a core feature of self-identity) and combat-related PTSD. The discovery of such mechanisms will offer a novel means for conceptualizing PTSD, and will ultimately provide information that drives future research and therapeutic innovations informed directly by basic science, which in turn, may help to mitigate negative outcomes associated with PTSD.

15. SUBJECT TERMS
Self-efficacy: one's perceived capacity to manage stressful life events.

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INTRODUCTION:

Changes in self-identity are associated with a greater risk of PTSD,[1] poor treatment prognosis,[2] and suicidal ideation.[3] Combat appears to have a lasting impact on the identity of individuals deployed to war zones. This proposal seeks to employ theories and paradigms from cognitive neuroscience to identify cognitive and neurobiological mechanisms underlying the relation between changes in self-efficacy (a core feature of self-identity) and combat-related PTSD. The substantial number of individuals with PTSD that remain symptomatic post-treatment indicates the presence of pathological mechanisms that have yet to be examined or fully understood. Therefore, studies targeting the basic cognitive mechanisms and neurobiology of PTSD are a necessary first step in clarifying factors associated with risk in the onset and maintenance of PTSD. This study includes an analog and clinical phase (Phase 1 and Phase 2 respectively). In Phase 1, 120 healthy, civilian participants receive a self-efficacy induction, after which their affective responses to a trauma-film paradigm are monitored and their fear circuitry activation is examined using fMRI. Phase 2 consists of 4 experiments with 300 OEF/OIF veterans examining their self-efficacy, autobiographical remembering, future imagining, anticipatory fear and emotional expression using both behavioral and neuroimaging paradigms. These findings have the potential to deliver information that drives future research in therapeutic innovations and resilience training informed directly by basic science, which in turn, may help to mitigate negative outcomes associated with combat-related PTSD.

GOALS:

The major goals of this study are:

1. Test whether increasing perception of self-efficacy reduces maladaptive cognitive and affective responses following exposure to a trauma film video.

2. Examine the neural basis of affect regulation by increasing perceptions of self-efficacy during fMRI tasks among healthy control participants

3. Examine the cognitive processes and neural activation patters associated with memory and future thinking in PTSD

4. Examine the neural basis of affect regulation by increasing perceptions of self-efficacy during fMRI tasks among OEF/OIF veterans with and without PTSD

PROJECT ACCOMPLISHMENTS:

The Basic Cognitive Neuroscience of Self-Appraisals and Memory in PTSD study has completed the development phase, a majority of the implementation phase, and data analysis and manuscript preparation are underway. In Year 2 of the grant we accomplished several milestones and goals outlined in the Statement of Work. Our success in meeting these goals is detailed below.

1. **IRB**

We secured IRB approval from all regulatory sites including NYU School of Medicine and the DOD.

2. Personnel

The research team has been trained in all study procedures. The research team meets weekly to review the study's progress. Dr. Brown speaks with the staff on a daily basis. Consultants are contacted as needed and are updated regularly on the progress of the study.

Nadia Rahman was hired as a Research Data Associate. She replaced Nicole Kouri. Nadia Rahman has been fully trained in all aspects of her position.

3. Subject Recruitment, Enrollment and Completion

Subject recruitment and testing for the Phase 1 analog studies (Phase 1, Study 1 and Phase 1, Study 2) has been completed. Subject recruitment and testing for Phase II Study 1 and Phase II Study 2 with OEF/OIF veterans has been completed. OEF/OIF Veterans are currently being recruited and are participating in Phase II Experiments 3, and 4. OEF/OIF Veterans are being recruited from the DoD funded Biomarkers for PTSD study, the Steven and Alexandra Cohen Veterans Center for the Study for Post-Traumatic Stress Disorder and Traumatic Brain injury, and the community.

Table 1. Subject Recruitment, Enrollment and Completion Data

Experiment	**Recruited Subjects**	**Screened Subjects**	**Eligible Subjects**	**Ineligible Subjects**	**Enrolled Subjects**	**Completed Subjects**
Phase 1, Exp. 1	180	76	66	114	66	60
Phase 1, Exp. 2	173	64	40	128	45	40
Total Non-clinical	**227**	**140**	**106**	**242**	**111**	**100**
	Recruited Subjects	**Screened Subjects**	**Eligible Subjects**	**Ineligible Subjects**	**Enrolled Subjects**	**Completed Subjects**
Phase 2, Exp. 1	60	0	60	0	60	60
Phase 2, Exp. 2	33	31	38	9	64	40
Phase 2, Exp. 3	35	31	39	2	66	41
Phase 2, Exp. 4	31	31	36	3	62	39
Total Clinical	**159**	**93**	**173**	**14**	**252**	**180**
Total	**386**	**233**	**279**	**256**	**363**	**280**

4. Database Construction and Tracking

A secure database has been developed. All clinical assessment data from the self-report and neurocognitive measures for all participants in Experiments 1 and 2 of Phase 1 and Experiment 1, and 2, of Phase 2 have. All obtained data has ben cleaned and entered as digital data directly into the study secure database server. All neuroimaging data for all participants in Experiment 2 of Phase 1 and Experiments 2 and 3 in Phase II have been transferred to the study secure database server and is currently being analyzed using the FSL neuroimaging software.

5. Acquisition of Study procedures

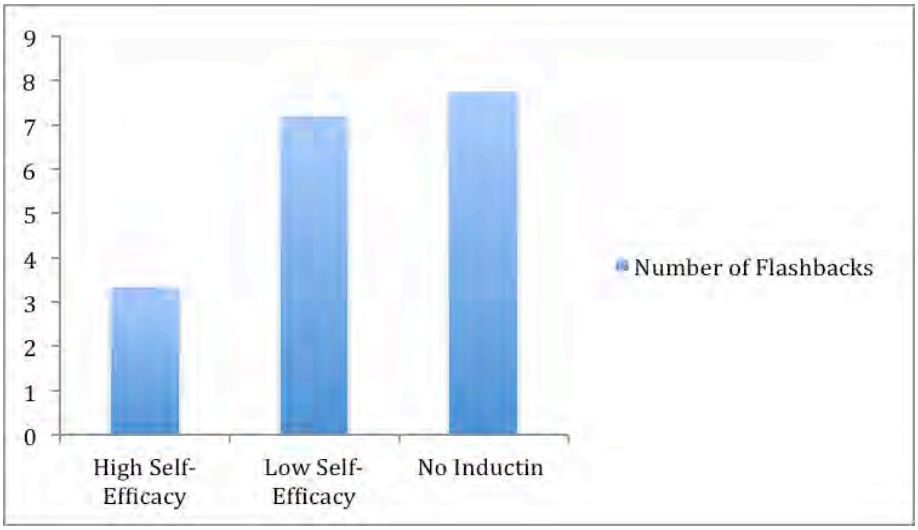
Study procedures used in Experiments 1 and 2 of Phase 1 including MRI imaging have been implemented and completed. Study procedures used in Experiments 1 and 2 of Phase 2 have been implemented and completed. Experiments 3 and 4 are are completely operational.

6. Standard Operating Procedure (SOP) Manuals

SOPs have been developed for Experiments 1 and 2 of Phase 1, and Experiments 1-4 of Phase 2.

7. Preliminary Analysis

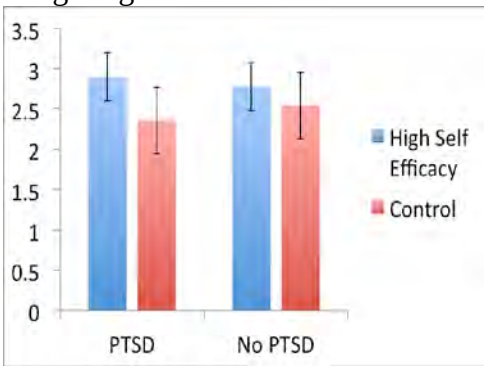
Phase 1, Experiment 1: 60 healthy volunteers have completed this experiment. Participants were randomly assigned to the High Self-Efficacy condition (N = 20), the Low Self-Efficacy condition (N = 20) and the Neutral Self-Efficacy condition (N = 20). The data has been entered into the study secure database server and the preliminary analyses have been completed. The findings indicate that individuals that received the self-efficacy induction showed significantly fewer trauma analog flashbacks over the course of 7 days.



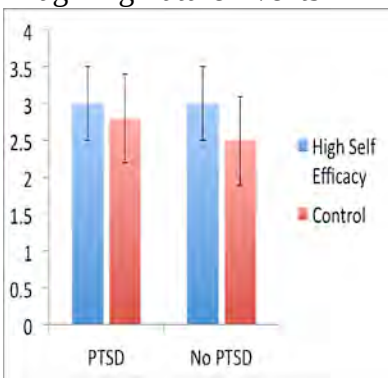
Phase 1, Experiment 2: Analysis of neuroimaging data for 40 subjects is underway, and we have established that we are getting results that suggest that the paradigm is working and that we are successfully acquiring neuroimaging data. The experimental task exposes participants to time intervals when they may receive mild electrical shocks, and other intervals when they know they will not receive any shocks. Analysis of neuroimaging data shows robust group-level activation in visual cortex in response to changing visual stimuli. Additional group means of interest include significant levels of deactivation in ventromedial PFC during the shock-related intervals. (This deactivation is also significantly lower than that seen in the non-shock-related trials) We have also begun to examine the effects of our self-efficacy induction on brain activity.

Phase 2, Experiment 1: OEF/OIF veterans were randomized to either a High Self Efficacy or Control condition. In the High Self Efficacy condition, individuals were asked to recall three autobiographical memories associated with success and self-efficacy. In the Control condition, participants recalled any three personally significant memories. After this task, participants completed a future thinking task in which they were given positive and negative cue words and were asked to imagine future events. In addition they were asked to complete two social problem-solving tasks. Specifically, participants listened to two military-related vignettes in which a protagonist is confronted with a specific problem or issue to be resolved. Based on the scoring system of the Means End Problem Solving Task (MEPS, Platt & Spivack, 1975) quantitative scores were computed for relevant means (discrete steps that enable the protagonist to move closer to the goal). Consistent with the hypotheses stated in the grant, preliminary analyses reveal that OEF/OIF individuals in the High Self-Efficacy condition (with and without PTSD) generated more positive future events and preformed better on indices of social problem solving and task (see results presented in Figure 2).

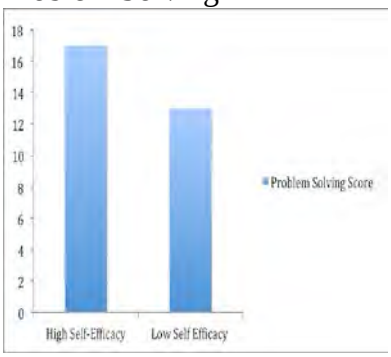
Number of Self Efficacy Statements when Imagining Future Events



Number of Positive Words when Imagining Future Events

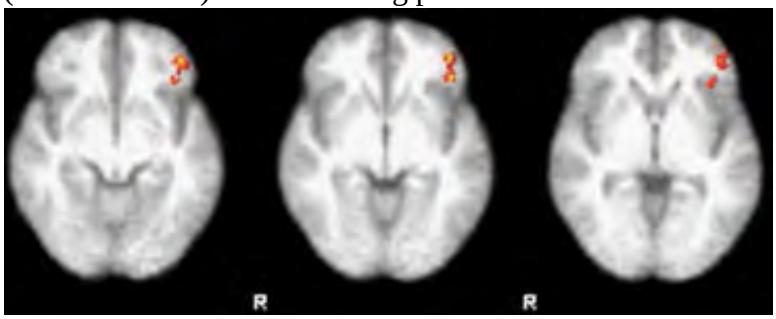


Number of Steps Generated when Problem Solving

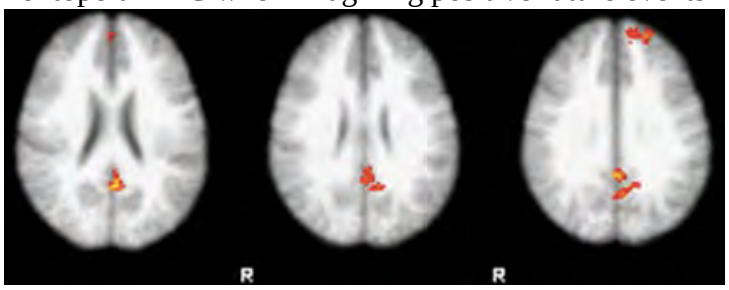


Phase 2, Experiment 2: OEF/OIF veterans with and without PTSD are presented with 80 cue words while undergoing fMRI scanning. They are presented with either positive or negative words and asked to either recall a personal past event or generate an imagined future event. Preliminary data analysis is underway. Findings to date suggest that OEF/OIF veterans with PTSD show significantly less recruitment in areas associated with the construction of autobiographical memories. In particular, OEF/OIF veterans appears to show significantly less recruitment in these areas when attempting to recall or imagine future positive events.

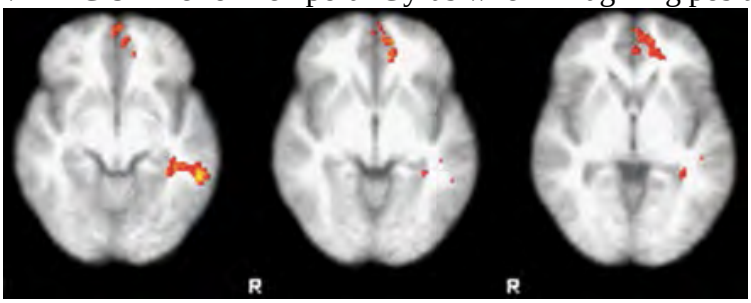
OEF/OIF Veterans with PTSD showed reduced activation in the Ventrolateral PFC (Left BA 10/47) when recalling positive memories



OEF/OIF Veterans with PTSD showed reduced activation in the Posterior Cingulate & Frontopolar PFC when imagining positive future events



OEF/OIF Veterans with PTSD showed reduced activation in the vmPFC & Inferior Temporal Gyrus when imagining positive future events



KEY RESEARCH ACCOMPLISHMENTS:

- Obtained IRB approvals across all sites and the DOD.
- Completed enrollment and testing for Phase 1 Experiments 1 and 2
- Completed enrollment and testing for Phase 2 Experiment 1 and 2
- Completed study procedures for, 47 OIF/OEF veterans in phase 2 experiment 2, 41 OIF/OEF in Phase 2 Experiment 3, and 39 OIF/OEF veterans in Phase 2 experiment 4.
- Research team participated in weekly study meetings.
- Entered, cleaned, and scored all data into a centralized database and ran reports for data analysis.
- Manuscript preparation is underway for Phase 1, Experiment 1 and Phase 2 Experiment 2.

CONCLUSION:

According to the Statement of Work, the tasks of months 12-24 of this study include:

1. Administer Analog Experiment 2 (months 8-14)
2. Administer Clinical Experiment 1 (months 10-16)
3. Administer Clinical Experiment 2 (months14-20)
4. Administer Clinical Experiment 3 (months 15-21)

5. Administer Clinical Experiment 4 (months 20-23)

Tasks (months 21-24):
6. Data Cleaning
7. Data Analysis
8. Manuscript Preparation
9. Dissemination

In Year 2 of the project we completed tasks 1 and 2. We have made significant progress with tasks 3 and 4. We have completed task 6 with all of the data obtained to date and task 7 is underway for Phase 1 Experiments 1 and 2, and Phase 2 Experiments 1 and 2. Manuscript preparation is underway for Phase 1 Experiment 1 and Phase 2 Experiment 1.

No Cost Extension:

A one year no-cost extension has been granted to complete the study extending the POP to January 15, 2016.

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