New Jersey Commission on Brain Injury Research
Final Narrative Report for Individual Research Grant

Glenn Wylie, D.Phil
300 Executive Drive, Suite 70
West Orange, NJ 07052
973-324-8452

KESSLER FOUNDATION

"Examination of Cognitive Fatigue in Traumatic Brain Injury using fMRI"

Grant Number:
10-3216-BIR-E-0

Grant Period:
6/1/10 – 5/31/14

Final Report Submitted on 7/30/14

Original aims of the project:
Fatigue is one of the most troubling symptoms in a variety of medical and neurological disorders including Traumatic Brain Injury (TBI), Multiple Sclerosis (MS), Chronic Fatigue Syndrome, and Cancer. In TBI, which has been estimated to occur in 1.5 million Americans annually [1], fatigue has a greater impact on the individual's life than any other factor [2]. In fact, fatigue is rated as the worst, or one of the worst, symptoms in 50% of those questioned [3]. Moreover, it is both pervasive and persistent—occurring in 45-73% of the TBI population [4, 5], with 73% of subjects reporting significant levels of fatigue even five years after the injury [4]. Indeed, in clinical populations such as MS, fatigue is the single most commonly reported symptom [6, 7], and one of the "most troubling symptom[s]" [8] experienced. *Cognitive fatigue*, in particular, has been reported to have a significant negative impact on the quality of life, including performance of everyday tasks [2, 9].

Despite its significant impact on the lives of individuals with TBI, the neural mechanisms of cognitive fatigue are poorly understood. It has proved difficult to develop objective assessments of cognitive fatigue; researchers have had to rely on subjective fatigue measures (reflecting subjects' perception of fatigue), which have consistently—in over 100 years of research—failed to correlate with objective behavioral performance. Our pilot research, carried out at both the Kessler Foundation Research Center and the University of Medicine and Dentistry of New Jersey (UMDNJ) has provided evidence that functional Magnetic Resonance Imaging (fMRI) may be used to objectively assess cognitive fatigue by examining changes in brain activity over time during sustained performance of a cognitive task. The overall aim of the current study is to examine whether objective cognitive fatigue (as assessed by changes in brain activity during a cognitive task) can be correlated to subjective measures of cognitive fatigue in persons with TBI.

The proposed study will utilize a novel and innovative approach to investigate the neural underpinnings of cognitive fatigue using fMRI in TBI by inducing cognitive fatigue and examining functional changes in the brain. We plan to induce cognitive fatigue in individuals with TBI through sustained performance of an attention task, a modified version of the Symbol Digit Modalities Task (mSDMT) [10] in the MRI scanner. After each block of this task, cognitive fatigue will be subjectively assessed using a Visual Analogue Scale of fatigue (VAS-F) [11] to determine whether increases in brain activity over time in predefined brain regions hypothesized to underlie cognitive fatigue are correlated with increased subjective cognitive fatigue over time. Additionally, the subjects will be given a "non-fatiguing" task that should not correlate with subjective fatigue.

Assessing cognitive fatigue objectively using functional brain activity is a new and unique approach to studying the elusive relationship between objective and subjective fatigue following neurological insult. This innovative approach, which has been applied with enormous success to better understand other subjective psychological constructs such as pain [12], may help future researchers to further examine the mechanisms of fatigue, as well as providing a way to assess cognitive fatigue in response to treatment.

<u>The aims of the current study are</u>:
1.) To establish fMRI as an objective measure of cognitive fatigue in individuals with TBI. This will be done by demonstrating that brain activity in a specific network of brain areas will increase over repeated performance of a cognitively fatiguing task to a greater extent in individuals with TBI, as compared with healthy controls (HCs). The Symbol Digit Modalities Task (mSDMT) [10] will be used for this purpose based on our pilot data. To show that the mSDMT is truly inducing cognitive fatigue, we will include a "non-fatiguing" task, which we do not expect to be related to subjective fatigue.
2.) To examine the relationship between the objective measure of cognitive fatigue (cerebral activity increases during performance of mSDMT in specific brain regions) with self-reported measures of fatigue, which will be gathered before and after each presentation of the mSDMT.

Project successes:
We have had great success with this project. Over the course of the three years of the grant (and one year of no-cost extension), we have tested 35 TBIs and 19 HCs. These numbers do not fully represent our productivity on the grant, since each participant was scanned twice. Thus, we conducted 70 total scans on TBIs and 38 total scans on HCs. We were able to achieve this despite very demanding inclusion criteria.

The aims of the grant were both concerned with using brain activation data, as measured by fMRI, as a way to better understand cognitive fatigue – a persistent problem in TBI. To achieve this, we asked subjects perform demanding cognitive tasks while in the scanner, as well as far less demanding control tasks. Each subject performed a demanding condition of the "n-back" working memory task (the 2-back condition) as well as the "0-back" condition, which is far less demanding. They also performed a task designed to investigate processing speed – the SDMT task. As with the n-back task, there were two versions of the SDMT: a difficult condition that was cognitively demanding, and a far less demanding control condition. Our hypothesis was that the demanding conditions of these tasks would cause greater fatigue in subjects than the easier conditions, and that the fatigue would be associated with activation a specific set of brain areas including the basal ganglia and

ventro-medial prefrontal cortex. We expected this to be shown for both tasks. However, the data showed that while this pattern did indeed emerge, it did so only for the working memory task. That is, individuals with TBI became fatigued while performing the working memory task, but not while performing the processing speed task. Moreover, the network of brain areas associated with fatigue was active only during the fatiguing working memory task.

This is important for several reasons. First, we have demonstrated that we can experimentally manipulate fatigue in the lab. This has proven very difficult to do in previous studies of fatigue. Second, we have shown that a network of brain areas is associated with the fatigue that we can elicit with the working memory task. These brain areas are not active during the non-fatiguing processing speed task. This shows that the activation in this network of brain areas is specifically related to fatigue. This is a very important finding (an important 'success' of the grant), since being able to experimentally manipulate fatigue, and to objectively measure it, are vital preconditions for the development of treatments for fatigue (see below).

Presentations:

Wylie, G.R. Using fMRI to study fatigue in multiple schlerosis and traumatic brain injury. Invited collocium at Boston VA.

Weaver, S., Genova, H., Chiaravalloti, N. & Wylie, G.R. Neural Correlates of Working Memory Deficits Following Traumatic Brain Injury. The annual meeting of the Cogntive Neuroscience Society, Boston, MA, 2014.

Wylie, G.R., Genova, H., DeLuca, J., & Chiaravalloti, N. An investigation of cognitive fatigue in Traumatic Brain Injury using functional magnetic resonance imaging. The 40th Annual Meeting International Neuropsychological Society, Montreal, QC, 2012.

Wylie, G.R., Genova, H., DeLuca, J., & Chiaravalloti, N. The functional architecture of cognitive fatigue in Traumatic Brain Injury. The Federal Interagency Conference on Traumatic Brain Injury, Washington, DC, 2011.

Publications:

Wylie, G.R., Dobryakova, E., DeLuca, J &.Genova, H. (in preparation) .Using fMRI to better understand fatigue in TBI: is there a fatigue network?

Dobryakova, E., Genova, H., DeLuca, J & Wylie, G.R. (in preparation). State vs. Trait fatigue: Fatigue at different time-scales matters.

Weaver, S., Genova, H., Chiaravalloti, N. & Wylie, G.R. (in preparation). An examination of the role of targets in the n-back working memory paradigm in TBI: targets matter.

Project challenges:

There were relatively few challenges associated with this project. This may be because we have been conducting similar projects in other patient populations, and therefore many of the logistics associated with running the experiment has been standardized. Recruitment is always challenging, but we were able to recruit sufficient numbers of subjects to show reliable effects. Moreover, we were able to get the vast majority of our subjects to return for a second scan, which was a great triumph.

Implications for future research and/or clinical treatment:

There are several implications of this work. One is that it is possible to study fatigue in TBI using brain activation as an objective measure of fatigue. This is itself a paradigm shift, inasmuch as all attempts to find reliable objective measures of fatigue in TBI have hitherto failed. Now that we have demonstrated that the BOLD signal can be used as an objective measure of fatigue, we can use this activation to study the effects of interventions designed to reduce fatigue. For example, we can assess whether a pharmaceutical intervention such as methylphenidate or a behavioral intervention such as exercise (both of which have been shown to reduce fatigue) have similar effects on the neural correlates of fatigue.

More broadly, this work shows that the same network of brain areas is associated with fatigue in TBI as has been implicated in fatigue in other populations such as multiple sclerosis and Parkinson's Disease. This strongly suggests that these areas are intimately involved in fatigue. From a theoretical standpoint, this may mean that these areas are called into action to combat fatigue – they are the same areas that are implicated in goal-directed learning, and they may therefore be related to subjects motivating themselves to continue performing the task despite their fatigue. Alternatively, these areas may provide something like a 'fatigue

signal', whereby the brain signals that enough resources have been expended on the task at hand, and that it is time to 'move on' (with a feeling of fatigue as the signal). These questions must await future research.

Plans to continue the research, including applications submitted to other sources for ongoing support. On the strength of our findings from this study, we have submitted several grant applications. We have submitted a VA grant to investigate fatigue in mild TBI, to see whether the same brain areas are associated with fatigue in mild TBI as in moderate/severe TBI. We have also submitted a VA grant to investigate whether transcranial direct current stimulation (tDCS) can be used to alleviate fatigue in moderate/severe TBI. In that application, we proposed to target the brain areas revealed in the work done here. We have also submitted a similar grant (to look at the effects of tDCS on fatigue in TBI) to the CDMRP.

Publications:

Wylie, G.R., Dobryakova, E., DeLuca, J &.Genova, H. (in preparation) .Using fMRI to better understand fatigue in TBI: is there a fatigue network?

Dobryakova, E., Genova, H., DeLuca, J & Wylie, G.R. (in preparation). State vs. Trait fatigue: Fatigue at different time-scales matters.

Weaver, S., Genova, H., Chiaravalloti, N. & Wylie, G.R. (in preparation). An examination of the role of targets in the n-back working memory paradigm in TBI: targets matter.

Financial Reporting. (Attached)

CR345

New Jersey Department of Health and Senior Services
REPORT OF GRANT EXPENDITURES

Reporting Agency: Kessler Foundation	Grant Number: 10-3216-BIR-E-0	Reporting Period: FROM: 01/1/14 TO: 03/31/14	Report Number: 16
Address: 300 Executive Drive-Suite 10	Grantee Account/Fund Number: 46.00457	Budget Period: FROM: 6/01/10 TO: 5/31/14	Revision Report No.
City: West Orange, NJ 07052	NJDHSS Account Number(s): 4029-457-6140	Basis of Report: ☐ CASH ☒ ACCRUAL	☒ FINAL
Grant Title: Examination of Cognitive Fatigue in TBI Using FMRI			

ROUND OFF TO NEAREST DOLLAR

BUDGET CATEGORIES	APPROVED BUDGET		PERIOD EXPENDITURES		CUMULATIVE EXPENDITURES	
	Grant Funds	Other Funds	Grant Funds	Other Funds	Grant Funds	Other Funds
A. PERSONNEL COST						
Salaries/Wages	235,126		18,468		278,300	
Fringe Benefits						
Total	235,126		18,468		278,300	
B. CONSULTANT/PROFESSIONAL SERVICES COST	.00		.00		.00	
Total	.00		.00		.00	
C. OTHER COST CATEGORIES						
Office Expense and Related Cost	4,000		31		671	
Program Expense and Related Cost	93,908		3,289		55,196	
Staff Training and Education Cost	.00		.00		.00	
Travel, Conferences and Meetings	4,500		45		5,408	
Equipment and Other Capital Expenditures	3,000		.00		959	
Facility Cost	.00		.00		.00	
Sub-Grants	.00		.00		.00	
Total	105,408		3,365		62,234	
Total Direct Cost	340,534		21,833		340,534	
Indirect Cost	33,754		2,015		33,754	
Total Cost	374,288		23,848		374,288	
Less Program Income	.00		.00		.00	
NET TOTAL COST	374,288		23,848		374,288	

I certify this report is true and correct and all expenditures reported herein have been made in accordance with the terms and conditions of this grant and are properly reflected in the grantee's accounting records.

Name of Chief Financial Officer: Anne E. Ammons

Title: SrVP - Finance & CFO

Signature: Anne E Ammons Date: 04-20-14

Accepted By:

Grants Management Officer: Yes ☐ No ☐

Signature _____ Date _____

Status of Funds:

Cash received to date	$ 350,440
Less: 03-31-14	
Cash disbursements as of 03-31-14 (Date)	$ 374,288
Cash Balance as of 03-31-14 (Date)	$ (23,848)

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