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	5c. PROGRAM ELEMENT NUMBER 611102

6. AUTHORS Benzi Kluger, Mingzhou Ding, Donald Rojas, Lauren Krupp, Roger Enoka	5d. PROJECT NUMBER
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7. PERFORMING ORGANIZATION NAMES AND ADDRESSES University of Colorado - Denver Mail Stop F428, Anschutz Medical Campus, Building : 13001 E. 17th Place, Room W1126 Aurora, CO 80045 -2571	8. PERFORMING ORGANIZATION REPORT NUMBER
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13. SUPPLEMENTARY NOTES The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision, unless so designated by other documentation.

14. ABSTRACT Specific Aims: 1) To identify and characterize the functional neuroanatomic networks most strongly correlated with objective cognitive fatigue using event related potentials (ERPs). 2) To determine the neurophysiologic mechanisms underlying objective cognitive fatigue using the variable signal plus ongoing activity (VSPOA) model. 3) To investigate the relationship of GABAergic and glutamatergic neural transmission to objective cognitive

15. SUBJECT TERMS cognitive, fatigue, fatigability, magnetoencephalography, transcranial magnetic stimulation
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16. SECURITY CLASSIFICATION OF:	17. LIMITATION OF ABSTRACT	15. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT UU	UU		Benzi Kluger
b. ABSTRACT UU			19b. TELEPHONE NUMBER 303-724-4400
c. THIS PAGE UU			

Report Title

Final Report: Study of the Neurophysiology of Central Fatigue

ABSTRACT

Specific Aims:

- 1) To identify and characterize the functional neuroanatomic networks most strongly correlated with objective cognitive fatigue using event related potentials (ERPs).
- 2) To determine the neurophysiologic mechanisms underlying objective cognitive fatigue using the variable signal plus ongoing activity (VSPOA) model.
- 3) To investigate the relationship of GABAergic and glutamatergic neural transmission to objective cognitive fatigue and network pathology.

Results of Findings:

- 1) We have developed a novel unifying taxonomy to clarify and standardize fatigue and fatigability terminology for research. (Manuscript published)
 - 2) We have found that intraindividual variability (performance variability) is a more sensitive indicator of behavioral fatigability than change in response time or accuracy. (Manuscript published)
 - 3) We have found that behavioral and physiological markers of cognitive control are impacted by prolonged cognitive task performance and mediate many performance changes. (Abstract published, manuscript under review)
 - 4) Single trial ERP analyses reveal that noise (jitter) and amplitude changes both contribute to reductions in ERPs seen with prolonged cognitive performance. (manuscript in preparation)
 - 5) Slowing of oscillatory activity, particularly in alpha frequencies, occurs over prolonged task and correlates with task performance. (manuscript in preparation)
 - 6) We have identified ERP markers of compensation to fatigue. (manuscript in preparation)
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Enter List of papers submitted or published that acknowledge ARO support from the start of the project to the date of this printing. List the papers, including journal references, in the following categories:

(a) Papers published in peer-reviewed journals (N/A for none)

<u>Received</u>	<u>Paper</u>
08/28/2012 4.00	Candace Palmer, Johanna T. Shattuck, William J. Triggs, Benzi M. Kluger. Motor evoked potential depression following repetitive central motor initiation, Experimental Brain Research, (12 2011): 585. doi: 10.1007/s00221-011-2962-y
TOTAL:	1

Number of Papers published in peer-reviewed journals:

(b) Papers published in non-peer-reviewed journals (N/A for none)

<u>Received</u>	<u>Paper</u>
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TOTAL:

Number of Papers published in non peer-reviewed journals:

(c) Presentations

Number of Presentations: 0.00

Non Peer-Reviewed Conference Proceeding publications (other than abstracts):

Received Paper

TOTAL:

Number of Non Peer-Reviewed Conference Proceeding publications (other than abstracts):

Peer-Reviewed Conference Proceeding publications (other than abstracts):

Received Paper

TOTAL:

Number of Peer-Reviewed Conference Proceeding publications (other than abstracts):

(d) Manuscripts

Received Paper

08/28/2012 3.00 Lauren B. Krupp, Benzi M. Gluger, Roger M. Enoka. Fatigue and Fatigability in Neurological Illnesses: Review and Proposal for a Unified Taxonomy, Neurology (08 2012)

11/05/2014 5.00 Chao Wang, Mingzhou Ding, Benzi Kluger. Change in intraindividual variability over time as a key metric for defining performance-based cognitive fatigability., Brain and Cognition (01 2014)

TOTAL: 2

Number of Manuscripts:

Books

Received Book

TOTAL:

Received Book Chapter

TOTAL:

Patents Submitted

Patents Awarded

Awards

Graduate Students

<u>NAME</u>	<u>PERCENT SUPPORTED</u>	<u>Discipline</u>
Chao Wang	0.40	
FTE Equivalent:	0.40	
Total Number:	1	

Names of Post Doctorates

<u>NAME</u>	<u>PERCENT SUPPORTED</u>
FTE Equivalent:	
Total Number:	

Names of Faculty Supported

<u>NAME</u>	<u>PERCENT SUPPORTED</u>	National Academy Member
Benzi Kluger	0.15	
FTE Equivalent:	0.15	
Total Number:	1	

Names of Under Graduate students supported

<u>NAME</u>	<u>PERCENT SUPPORTED</u>
FTE Equivalent:	
Total Number:	

Student Metrics

This section only applies to graduating undergraduates supported by this agreement in this reporting period

The number of undergraduates funded by this agreement who graduated during this period: 0.00

The number of undergraduates funded by this agreement who graduated during this period with a degree in science, mathematics, engineering, or technology fields:..... 0.00

The number of undergraduates funded by your agreement who graduated during this period and will continue to pursue a graduate or Ph.D. degree in science, mathematics, engineering, or technology fields:..... 0.00

Number of graduating undergraduates who achieved a 3.5 GPA to 4.0 (4.0 max scale):..... 0.00

Number of graduating undergraduates funded by a DoD funded Center of Excellence grant for Education, Research and Engineering:..... 0.00

The number of undergraduates funded by your agreement who graduated during this period and intend to work for the Department of Defense 0.00

The number of undergraduates funded by your agreement who graduated during this period and will receive scholarships or fellowships for further studies in science, mathematics, engineering or technology fields:..... 0.00

Names of Personnel receiving masters degrees

<u>NAME</u>
Total Number:

Names of personnel receiving PHDs

<u>NAME</u>
Chao Wang
Total Number:

Names of other research staff

<u>NAME</u>	<u>PERCENT SUPPORTED</u>
Johanna Shattuck	0.50
FTE Equivalent:	0.50
Total Number:	1

Sub Contractors (DD882)

Inventions (DD882)

Scientific Progress

Scientific Progress and Accomplishments

Since the beginning of this project we have made the following scientific progress:

- 1) We have developed a novel unifying taxonomy to clarify and standardize fatigue and fatigability terminology for research. 1
- 2) We have found that intraindividual variability (performance variability) is a more sensitive indicator of behavioral fatigability than change in response time or accuracy. We have also found on the basis of reaction time (RT) distributions that RT outliers drive apparent slowing in fatigue tasks.2
- 3) We have found that behavioral and physiological markers of cognitive control are impacted by prolonged cognitive task performance and mediate many performance changes. (Abstract published, manuscript under review)3, 4
- 4) Single trial ERP analyses reveal that noise (jitter) and amplitude changes both contribute to reductions in ERPs seen with prolonged cognitive performance. (manuscript in preparation)
- 5) Slowing of oscillatory activity, particularly in alpha frequencies, occurs over prolonged task and correlates with task performance. Contrary to our initial predictions, coherence, particularly in lower frequencies, also increases over the course of prolonged performance. (manuscript in preparation)
- 6) We have identified ERP markers brain activity specifically engaged for compensation of mental fatigue. (abstract under review, manuscript in preparation)

Citations

1. Kluger BM, Krupp LB, Enoka RM. Fatigue and fatigability in neurologic illnesses: Proposal for a unified taxonomy. *Neurology* 2013;80:409-416.
2. Wang C, Ding M, Kluger BM. Change in intraindividual variability over time as a key metric for defining performance-based cognitive fatigability. *Brain and Cognition* 2014;85:251-258.
3. Kluger B, Wang C, Proemsey J, Ding M. Neuronal Correlates of Executive Dysfunction and Fatigability in Parkinson Disease. *Movement Disorders* 2012;27:e6.
4. Wang C, Ding M, Kluger BM. High-density EEG study of cue-evoked preparatory activity in a cued Stroop task. 2013 Neuroscience Meeting Planner San Diego, CA: Society for Neuroscience 2013;Online.

Technology Transfer

Scientific Progress and Accomplishments

Since the beginning of this project we have made the following scientific progress:

- 1) We have developed a novel unifying taxonomy to clarify and standardize fatigue and fatigability terminology for research. ¹
- 2) We have found that intraindividual variability (performance variability) is a more sensitive indicator of behavioral fatigability than change in response time or accuracy. We have also found on the basis of reaction time (RT) distributions that RT outliers drive apparent slowing in fatigue tasks.²
- 3) With our primary task (cued Stroop) we have found 4 topographically and functionally distinct ERP markers of proactive cognitive control. (manuscript under review)
- 4) We have found that behavioral and physiological markers of cognitive control are impacted by prolonged cognitive task performance and mediate many performance changes. (Abstract published, manuscript under review)^{3, 4}
- 5) Single trial ERP analyses reveal that noise (jitter) and amplitude changes both contribute to reductions in ERPs seen with prolonged cognitive performance. (manuscript in preparation)
- 6) Slowing of oscillatory activity, particularly in alpha frequencies, occurs over prolonged task and correlates with task performance. Contrary to our initial predictions, coherence, particularly in lower frequencies, also increases over the course of prolonged performance. (manuscript in preparation)
- 7) We have identified ERP markers brain activity specifically engaged for compensation of mental fatigue. (abstract under review, manuscript in preparation)

Citations

1. Kluger BM, Krupp LB, Enoka RM. Fatigue and fatigability in neurologic illnesses: Proposal for a unified taxonomy. *Neurology* 2013;80:409-416.
2. Wang C, Ding M, Kluger BM. Change in intraindividual variability over time as a key metric for defining performance-based cognitive fatigability. *Brain and Cognition* 2014;85:251-258.
3. Kluger B, Wang C, Proemsey J, Ding M. Neuronal Correlates of Executive Dysfunction and Fatigability in Parkinson Disease. *Movement Disorders* 2012;27:e6.
4. Wang C, Ding M, Kluger BM. High-density EEG study of cue-evoked preparatory activity in a cued Stroop task. 2013 Neuroscience Meeting Planner San Diego, CA: Society for Neuroscience 2013;Online.