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Award Number: DAMD17-01-1-0764

TITLE: Magnetic Resonance and Spectroscopy of the Human Brain in Gulf War Illness

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REPORT DATE: August 2005

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

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1. REPORT DATE (DD-MM-YYYY) 01-08-2005		2. REPORT TYPE Annual		3. DATES COVERED (From - To) 1 Aug 2004 – 31 Jul 2005	
4. TITLE AND SUBTITLE Magnetic Resonance and Spectroscopy of the Human Brain in Gulf War Illness				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER DAMD17-01-1-0764	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Michael W. Weiner, M.D. E-mail: mweiner@itsa.ucsf.edu				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Northern California Institute for Research and Education San Francisco, CA 94121				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT The goal of this project is to test the hypotheses that: 1) Subjects with GWI have reduced NAA in the basal ganglia and pons, which are not accounted for by confounds such as PTSD, depression, and alcohol abuse. 2) Reduced NAA in basal ganglia and pons correlates with CNS signs and symptoms of GWI. Study procedures include a medical evaluation, clinical assessments, neurocognitive testing, startle testing, MRI/MRSI, and the "Haley Questionnaire." To date, we have studied a total of 253 subjects, 225 of whom have data for analysis. Of this total, 52 met criteria for GWI, 90 are controls, and 83 have an intermediate classification. Some preliminary data analysis has been performed.					
15. SUBJECT TERMS Gulf war illness, gulf war syndrome, magnetic resonance imaging, magnetic resonance spectroscopy, human brain, neuro-psychological testing, audio vestibular testing, PTSD					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	11	19b. TELEPHONE NUMBER (include area code)

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INTRODUCTION

The primary goal of this project is to test the *a priori* hypotheses that: 1) Subjects with Gulf War Illness (GWI) have reduced N-acetyl aspartate (NAA) in the basal ganglia and pons, which are not accounted for by confounds such as PTSD, depression, or alcohol abuse. 2) Reduced NAA in the basal ganglia and pons correlates with central nervous system signs and symptoms of GWI. This project proposes to replicate and extend previous findings of Haley et al. on 200 subjects with GWI and 200 Gulf War Veteran (GWV) controls drawn from Northern California and its surrounding regions. To date we have recruited 302 subjects, and enrolled 253 into the study. Of these, 225 have met inclusion criteria. Current efforts are aimed at increasing enrollment of GWI. We continue to mail recruitment letters to Gulf War veterans residing in California and Nevada at the rate of 1000 per month.

RESULTS

Thus far, 225 subjects have data for analysis. Subjects are categorized as GW Veterans (healthy controls), GW Illness (those who meet CDC criteria), or intermediate (those with an inconsistent symptom presentation). Table 1 summarizes our demographic variables. "CAPS current" represents the mean score of the frequency and severity of the Clinician Administered PTSD Scale on a scale from 0-4 for 17 symptoms of posttraumatic stress. "Current drinking" represents the mean number of alcoholic drinks consumed monthly. "GWI severity" represents the mean score of Gulf War Illness as measured by a medical practitioner's clinical judgment.

Table 1: Demographics

	GW Veteran	Intermediate	GW Illness
N	90	83	52
Age	44.18 ± 9.9	44.58 ± 10.5	42.02 ± 8.7
Education	14.73 ± 2.1	14.60 ± 3.0	14.15 ± 1.7
CAPS Current	5.70 ± 11.9	17.64 ± 22.2	26.06 ± 23.4
Current Drinking	11.88 ± 18.2	25.00 ± 79.6	8.15 ± 14.3
GWI Severity	1.75 ± 0.5	1.79 ± 0.9	2.81 ± 1.0

Haley Factor Analysis

Subjects completed the identical questionnaire as designed by Haley et al. Furthermore, the data was analyzed using software provided by Dr. Haley. Table 2 summarizes the number of syndrome two subjects in our study.

Table 2: Haley Syndrome II

Classification	Syndrome II	Not Syndrome II
GW Veteran	2 (1)	66 (8)
Intermediate	8 (1)	56 (3)
GW Illness	15 (5)	28 (6)

In braces are number of female subjects

Spectral Data Analysis

NAA is a measure of neuronal density or integrity and can be measured as absolute NAA or a ratio to other metabolites. The following tables present preliminary spectral data. Thus far the MRS studies do not support Haley's previous results that NAA is reduced in GWI. These analyses have not controlled for the effects of PTSD, depression, and alcohol consumption.

Table 3: Left Basal Ganglia
(male subjects only)

	n	NAA/Cre	NAA/Cho	Cho/Cre	NAA/(Cho+Cre)
Vets	47	1.66 ± 0.12	4.58 ± 0.44	0.36 ± 0.03	1.22 ± 0.09
Intermediates	37	1.62 ± 0.17	4.79 ± 0.61	0.34 ± 0.04	1.21 ± 0.12
Illness	24	1.67 ± 0.12	4.77 ± 0.51	0.35 ± 0.04	1.24 ± 0.08
Vets vs. Illness		n.s.	0.11	n.s.	n.s.
Vets vs. Intermediates		n.s.	n.s.	n.s.	n.s.
Intermediates vs. Illness		n.s.	n.s.	n.s.	n.s.

Table 4: Right Basal Ganglia
(male subjects only)

	n	NAA/Cre	NAA/Cho	Cho/Cre	NAA/(Cho+Cre)
Vets	43	1.59 ± 0.20	4.29 ± 0.49	0.37 ± 0.03	1.16 ± 0.13
Intermediates	33	1.54 ± 0.51	4.30 ± 0.57	0.36 ± 0.05	1.13 ± 0.11
Illness	20	1.59 ± 0.18	4.47 ± 0.47	0.36 ± 0.04	1.17 ± 0.12
Vets vs. Illness		n.s.	n.s.	n.s.	n.s.
Vets vs. Intermediates		n.s.	n.s.	n.s.	n.s.
Intermediates vs. Illness		n.s.	n.s.	n.s.	n.s.

Table 5: Pons
(male subjects only)

	n	NAA/Cre	NAA/Cho	Cho/Cre	NAA/(Cho+Cre)
Vets	26	2.25 ± 0.39	0.66 ± 0.10	3.44 ± 0.46	1.36 ± 0.19
Intermediates	27	2.25 ± 0.32	0.62 ± 0.12	3.73 ± 0.72	1.39 ± 0.17
Illness	12	2.29 ± 0.69	0.63 ± 0.13	3.60 ± 0.63	1.39 ± 0.33
Vets vs. Illness		n.s.	n.s.	n.s.	n.s.
Vets vs. Intermediates		n.s.	n.s.	n.s.	n.s.
Intermediates vs. Illness		n.s.	n.s.	n.s.	n.s.

Table 6: Left Basal Ganglia
(controls vs. syndrome II, male subjects only)

	n	NAA/Cre	NAA/Cho	Cho/Cre	NAA/(Cho+Cre)
Veterans	47	1.66 ± 0.12	4.58 ± 0.44	0.36 ± 0.03	1.22 ± 0.09
Syndrome II	8	1.69 ± 0.12	4.94 ± 0.63	0.35 ± 0.04	1.25 ± 0.08
Syndrome II vs. Vets		n.s.	0.03	n.s.	n.s.

Table 7: Right Basal Ganglia
(controls vs. syndrome II, male subjects only)

	n	NAA/Cre	NAA/Cho	Cho/Cre	NAA/(Cho+Cre)
Veterans	43	1.59 ± 0.20	4.29 ± 0.49	0.37 ± 0.03	1.16 ± 0.13
Syndrome II	7	1.56 ± 0.17	4.60 ± 0.39	0.34 ± 0.04	1.16 ± 0.10
Syndrome II vs. Vets		n.s.	0.08	0.01	n.s.

Table 8: Pons
(controls vs. syndrome II, male subjects only)

	n	NAA/Cre	NAA/Cho	Cho/Cre	NAA/(Cho+Cre)
Veterans	26	2.25 ± 0.39	3.44 ± 0.46	0.66 ± 0.10	3.44 ± 0.46
Syndrome II	5	2.51 ± 0.65	3.84 ± 0.70	0.65 ± 0.10	3.84 ± 0.70
Syndrome II vs. Vets		n.s.	n.s.	n.s.	n.s.

Neurocognitive Assessment

Haley et al. reported global intellectual and neurocognitive dysfunction among ill veterans when compared to control veterans. This study administered tests similar to those used by Haley in an attempt to replicate his findings. Tests were combined into the following domains: verbal IQ (WAIS-III vocabulary, similarities, arithmetic, digit span, information and comprehension subtests), performance IQ (WAIS-III picture completion, digit symbol, and block design subtests), premorbid (WRAT-III reading subtest), executive function (COWAT and trail making test B), memory (CVLT long delay, BVMT retention, and logical memory retention), learning (CVLT immediate recall and BVMT immediate recall), auditory attention (WAIS-III digit span subtest), CPT attention (CPT commission errors), motor speed & dexterity (grooved pegboard and grip strength), processing speed (WAIS-III digit symbol and trail making test A), and motor balance (Fregly ataxia). Table 9 summarizes the preliminary data for our neurocognitive battery. Figure 1 illustrates motor balance performance.

Table 9: Neurocognitive Domains
(male subjects only)

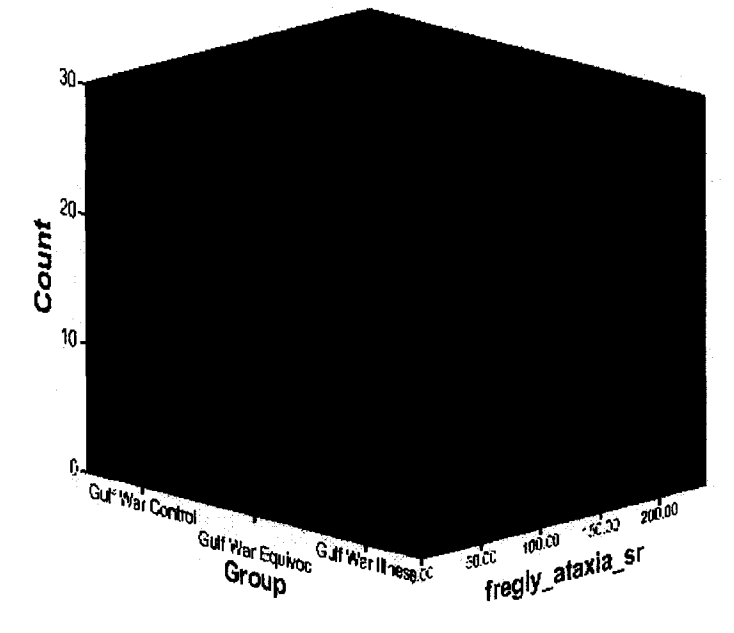
	GW Veteran	Intermediate	GW Illness
Verbal IQ (sum of scaled scores)	67.47 ± 14.8 n=48	61.13 ± 12.5 n=61	65.6 ± 10.5 n=30
Performance IQ (sum of scaled scores)	32.76 ± 7.6 [†] n=68	29.32 ± 6.4 n=68	30.02 ± 5.7 [†] n=35
Premorbid (z-scores)	.247 ± 1.00 n=68	-.13 ± 1.11 n=68	.094 ± .72 n=35
Executive Function (z-scores)	.050 ± .89 n=69	-.119 ± .76 n=68	.148 ± .60 n=34
Memory (z-scores)	.135 ± .68 n=60	-.133 ± .63 n=65	-.003 ± .52 n=34
Learning (z-scores)	.109 ± .82 n=60	-.119 ± .82 n=65	-.007 ± .89 n=34
Auditory Attention (z-scores)	.307 ± 1.03 n=68	-.014 ± .92 n=68	.511 ± .89 n=34
CPT Attention (raw scores)	10.53 ± 6.6* n=62	12.05 ± 8.2 n=64	15.75 ± 7.5* n=32
Motor Speed & Dexterity (z-scores)	.269 ± .63 n=68	-.062 ± .69 n=66	.160 ± .55 n=35
Processing Speed (z-scores)	.106 ± .91** n=69	-.128 ± .75 n=67	-.136 ± .71** n=34

[†]p=.09

*p=.001

**p<.05 when accounting for age

Figure 1: Fregly Ataxia, Sharpened Romberg
(male subjects only)



PTSD and Acoustic Startle Response

There is controversy over the relationship between GWI and stress. Acoustic startle is a hallmark feature of PTSD. Past studies have shown that PTSD subjects have an increased startle response, especially under fear conditions. Acoustic startle response was assessed both at baseline and under threat of electric shock. Figures 2-6 illustrate our preliminary findings.

Figure 2:
PTSD Symptoms in Healthy, Intermediate,
and Gulf War Syndrome Subjects

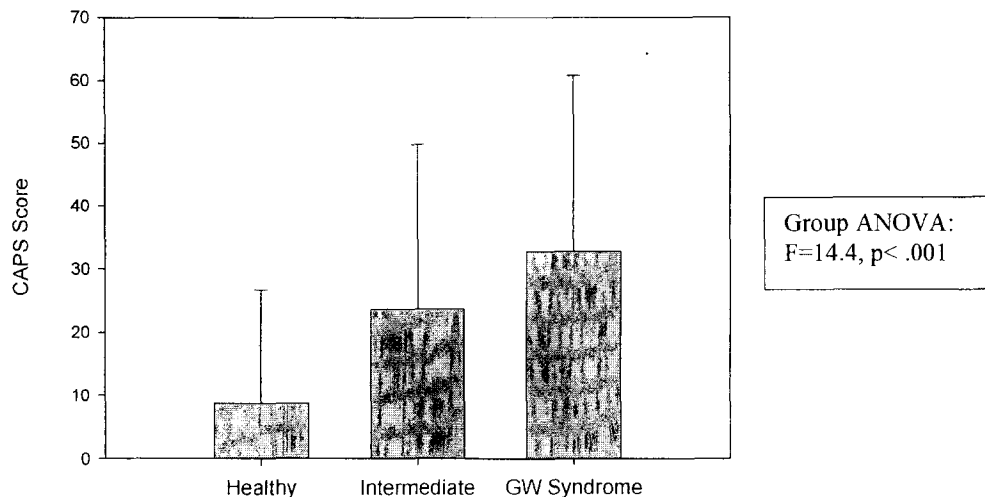


Figure 3:
Startle Response in Healthy and PTSD Subjects

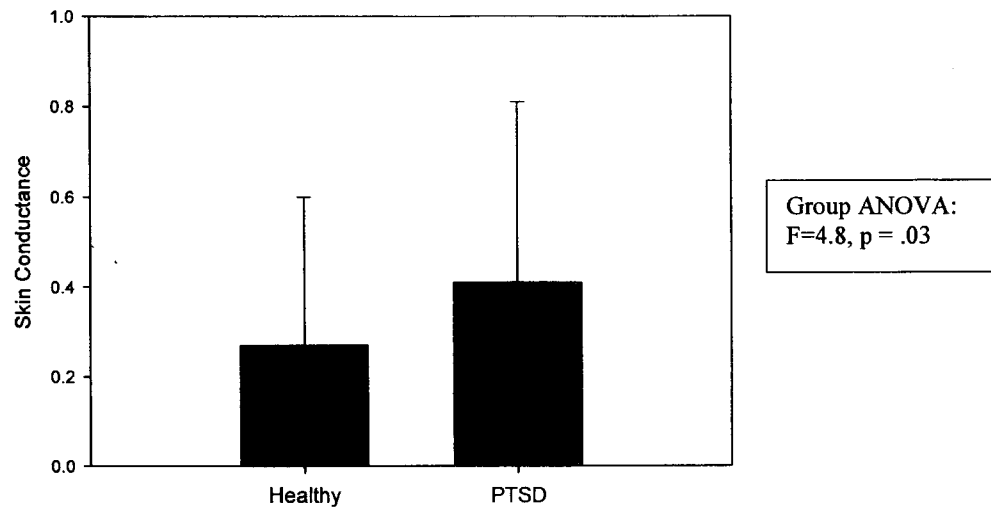


Figure 4:
Startle Response in Healthy and PTSD Subjects

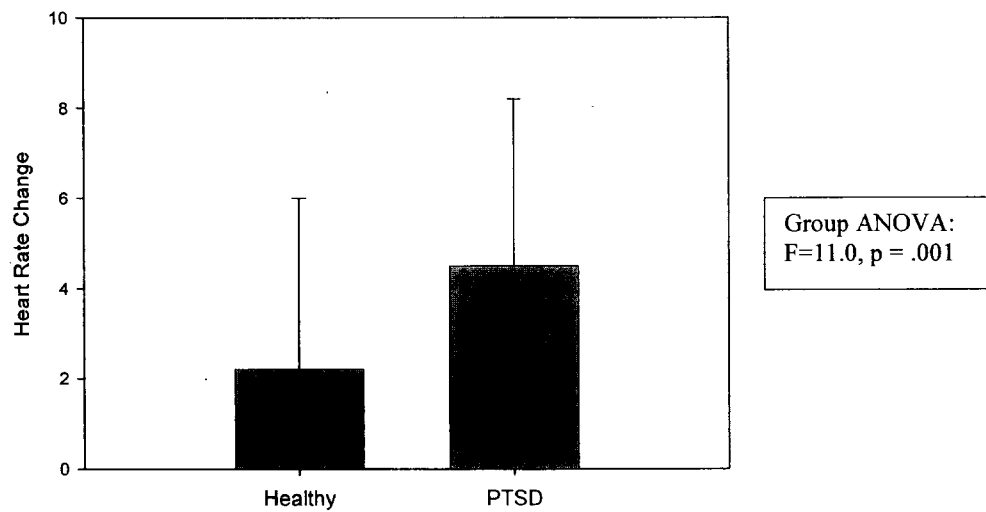


Figure 5:
Startle Response in Healthy, Intermediate,
and Gulf War Syndrome Subjects

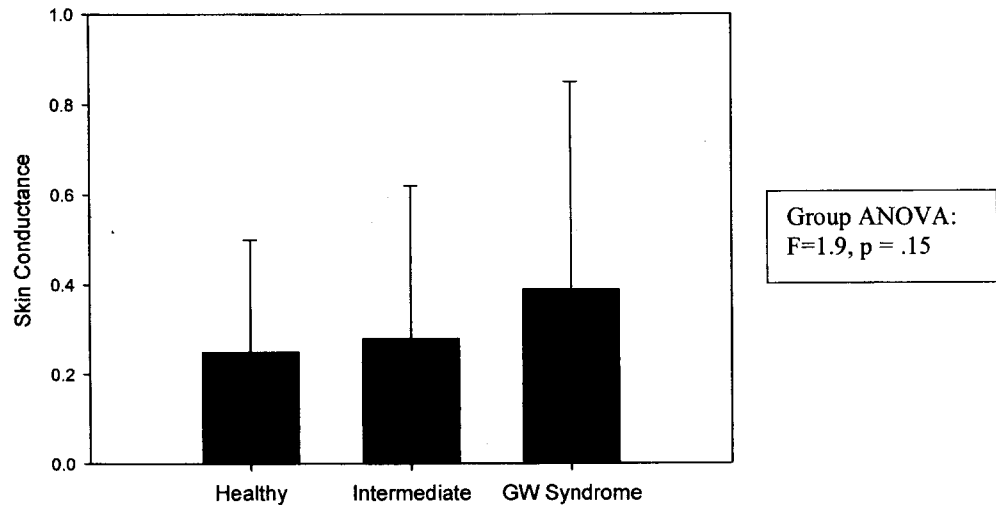
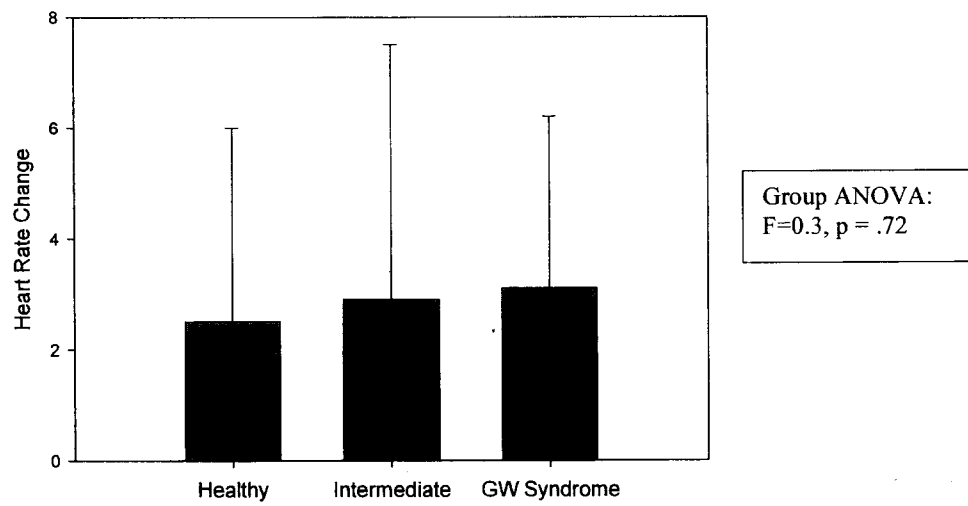


Figure 6:
Startle Response in Healthy, Intermediate,
and Gulf War Syndrome Subjects



KEY RESEARCH ACCOMPLISHMENTS

- New staff hired and trained.
- Study manuals and protocols maintained.
- UCSF, VA, and DOD IRB approvals maintained.
- Subjects entered into study: 253
- Continued preliminary analysis of data.
- Thus far no replication of Haley's results

REPORTABLE OUTCOMES

- No publications at this stage of the project.
- Meeting of Neuroimaging and Gulf War Veterans in the UK. Talk given by teleconference. Jan 24th, 2005.
- VA Headquarters in Washington, DC Meeting on Magnetic Resonance and Spectroscopy of Human Brain in Gulf War Illness. May 26th, 2003.
- NIH MR and Spectroscopy of Human Brain in Gulf War Illness Conference. Talk entitled "Magnetic Resonance and Spectroscopy of Human Brain in Gulf War Illness." February 19th, 2002.

CONCLUSIONS

After 3.5 years of data collection, the three study groups are well matched with respect to age and education level. The preliminary spectral data suggest there are generally no differences between groups in the basal ganglia bilaterally or pons. Acoustic startle response data show no differences between ill and healthy subjects. The preliminary neurocognitive data indicate possible group differences on measures of performance IQ, CPT attention, processing speed, and motor balance.

In summary, the results clearly show that we are able to recruit, study, and obtain usable data to meet the aims of this study. Although at this point in time, our data do not seem to replicate the findings of Haley et al., we do not have sufficient statistical power to derive any reliable conclusions. Further work is required, and we expect that the full 5 years of funding will be needed to obtain data to support robust conclusions.