A. OVERALL COVER PAGE

Project Title: World Trade Center Exposures, Neuropathic Symptoms and Nervous System Injury	
Grant Number: 5U01OH011305-02	**Project/Grant Period:** 09/01/2016 - 08/31/2018
Reporting Period: 09/01/2017 - 08/31/2018	**Requested Budget Period:** 09/01/2017 - 08/31/2018
Report Term Frequency: Annual	**Date Submitted:** 11/27/2019
Program Director/Principal Investigator Information: MICHAEL MARMOR , MA PHD **Phone number:** (212) 263-6667 **Email:** MICHAEL.MARMOR@NYULANGONE.ORG	**Recipient Organization:** NEW YORK UNIVERSITY SCHOOL OF MEDICINE One Park Avenue 6th Floor NEW YORK, NY 10016 **DUNS:** 121911077 **EIN:** 1135562309A1 **RECIPIENT ID:**
Change of Contact PD/PI: N/A	
Administrative Official: MORGAN MCNAMARA One Park Avenue New York, NY 10016 **Phone number:** 646-754-4614 **Email:** morgan.mcnamara@nyumc.org	**Signing Official:** ANTHONY CARNA 360 Park Avenue South 10th Floor New York, NY 10010 **Phone number:** (212) 263-8822 **Email:** grants.office@med.nyu.edu
Human Subjects:	**Vertebrate Animals:**
hESC: No	**Inventions/Patents:** No

B. OVERALL ACCOMPLISHMENTS

B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

The aims of the project were as follows:
Aim 1. To analyze associations of paresthesias at enrollment with World Trade Center (WTC) exposure variables, and to analyze longitudinal data on data on paresthesia.
Aim 2. To objectively measure neuropathy among members of the WTC Environmental Health Center (EHC) and investigate the association of these objective measures with self-reported neuropathic symptoms and WTC exposures while taking into account the results of blood tests for medical conditions and exposures to agents known to be associated paresthesias. Under this aim we proposed to evaluate risk factors for neuropathic symptoms via a case-control study in which cases were to be 40 WTC EHC patients with neuropathic symptoms, and controls were to be 40 WTC EHC patients free of neuropathic symptoms, frequency-matched to controls on age and gender; and absence of histories of diabetes, cancer chemotherpy and paresthesias prior to 9/11/2001. We also proposed to study a community-based control group of 20 individuals frequency-matched to cases on age and gender, and selected without regard for presence or absence of paresthsia. In all subjects, we performed standardized neurologic evaluations with questionnaires and clinical examinations including blood testing for pre-diabetes (via fasting glucose, hemoglobin A1C and comprehensive metabolic panel); syphilis; pernicious anemia (testing for B12 and methylmalonic acid); antinuclear antibody, to identify autoimmune disorders; ESR and C-reactive protein (CRP) to identify inflammation reactions; Lyme disease, because of the neuropathy associated with that diseases; serum protein electrophoresis (SPEP) with immunofixation; lead; and neuron-specific enolase, to identify central nervous system injury under the hypothesis that WTC microparticles may have migrated to the brain via the olfactory nerve. Among paresthesia cases, we also conducted skin punch biopsies to measure intra-epidermal nerve or sweat gland fiber densities, and nerve conduction studies.

B.1.a Have the major goals changed since the initial competing award or previous report?

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

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B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?

No

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

NOTHING TO REPORT

B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?

Progress has been reported at the World Trade Center Research Principal Investigators Meetings held semi-annually in New York City. Representatives of community groups concerned with World Trade Center health issues have been in attendance at these meetings.

B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

Not Applicable

Our activities during this reporting period included (a) data analysis and development of a publication using longitudinal data on paresthesia and (b) completion of data collection, data analysis and preparation of a manuscript for publication of our case-control study of paresthesia.

The specific aims of our project were (1) to analyze longitudinal data to describe the trajectories of paresthesias in the survivor population; (2) to analyze already-obtained electromyography/nerve conduction velocity (EMG/NCV) data in order to investigate the pathophysiology of the reported paresthesias; and (3) to examine via a case-control study whether neuropathic symptoms among Survivors were associated with abnormalities in nerve fiber densities or nerve conduction velocities, and whether they might be due not to WTC exposure, but to other medical conditions known to cause paresthesia. Our work focused on Survivors (with primarily non-rescue/recovery WTC exposures) enrolled in the WTC Environmental Health Center (WTC EHC), Bellevue Hospital, New York, NY.

In pursuit of Aim 1 we studied times to paresthesia among 3,411 WTC EHC patients. Paresthesia was defined as present if the symptom occurred in the lower extremities with frequency “often” or “almost continuous.” We plotted hazard functions and used the log-rank test to compare time to onset of paresthesia between different exposure groups. We also used Cox regression analysis to examine risk factors for time-to-paresthesia after 9/11/2001 and calculate hazard ratios adjusted for potential confounders. We found significantly elevated hazard ratios for paresthesia for (a) working in a job that required cleaning of WTC dust in the workplace; and (b) being heavily exposed to WTC dust on September 11, 2001, after adjusting for age, race/ethnicity, depression, anxiety, post-traumatic stress disorder, and body mass index. These data thus were consistent with the hypothesis that exposure to WTC dust or some other aspect of cleaning WTC dust in the workplace, led to development of associated with neuropathy and paresthesia.

In pursuit of Aim 2, we reviewed the electronic medical records of a sample of the ~80 individuals whose records had indicated referral for EMG/NCV. In a random sample of 10 of these patients, we found that 6 had never undergone this testing (having been referred, but never showing up for the testing), 3 had normal results, and 1 was found to have carpal tunnel syndrome, most likely not caused by WTC-associated factors. Due to these findings, Aim 2 was not further pursued.

In pursuit of Aim 3, we have completed a case-control study and submitted a manuscript for publication. The goal of the study was to investigate whether paresthesia of the lower extremities, commonly reported by individuals exposed to the World Trade Center (WTC) disaster of September 11, 2001, was associated with objective signs of neuropathy, metabolic abnormalities or neurotoxin exposures. We used a case-control design to compare paresthesia cases presenting at the Bellevue Hospital WTC Environmental Health Center (EHC) with “clinic controls” (WTC EHC clinic patients who did not report paresthesias), and “community controls” (persons unexposed to the WTC disaster). We contrasted 41 WTC EHC patients with neuropathic symptoms (“cases”) with 38 controls free of neuropathic symptoms. Controls were frequency-matched to cases on age and gender, and absence of histories of (a) paresthesia prior to 9/11/2001, (b) diabetes, (c) treatment with chemotherapeutic agents for cancer, (d)

treatment with antiretroviral drugs, (e) vitamin B12 deficiency, and (f) bleeding disorders and treatment with Coumadin or other blood thinners. In addition, a community-based control group of 20 individuals was enrolled to determine the prevalence of paresthesias and risk factors for paresthesias among similar, but non-WTC-exposed individuals. Subjects responded to questionnaires, had neurologic evaluations, and donated blood for analysis of hemoglobin A1c, fasting glucose, vitamin B12, methylmalonic acid, syphilis (VDRL); vitamin B12, methylmalonic acid, antinuclear antibody (ANA), C-reactive protein (CRP), Lyme disease antibodies, serum protein electrophoresis (SPEP) with immunofixation, celiac disease antibodies (i.e., antibodies to deamidated gliadin), and lead. Paresthesia cases had skin punch biopsies to obtain intra-epidermal nerve fiber density and sweat gland nerve fiber density, and nerve conduction studies. We found scores on the Norfolk Diabetic Neuropathy Quality of Life, the Utah Early Neuropathy Scale, the Michigan Neuropathy Screening Instrument, and a standardized neurological history and examination were significantly higher (worse) in cases than controls. Intraepidermal or sweat gland nerve fiber densities were abnormally low in 57% of cases; nerve conduction velocities were abnormally low in 3%. Neurologic abnormalities were uncommon among community controls. Parethesia cases did not have increased markers of diabetes, vitamin deficiencies, or other common etiologies of neuropathy. We concluded that paresthesias among WTC-exposed individuals were associated with increased signs of neuropathy and reduced small nerve fiber densities. The data support the hypothesis that WTC exposure was an independent risk factor for neuropathic symptoms, and did not support alternative, non-WTC etiologies.

C. OVERALL PRODUCTS

C.1 PUBLICATIONS

Are there publications or manuscripts accepted for publication in a journal or other publication (e.g., book, one-time publication, monograph) during the reporting period resulting directly from this award?

Yes

Publications Reported for this Reporting Period

Public Access Compliance	Citation
N/A: Not NIH Funded	Marmor M, Shao Y, Bhatt DH, Stecker MM, Berger KI, Goldring RM, Rosen RL, Caplan-Shaw C, Kazeros A, Pradhan D, Wilkenfeld M, Reibman J. Paresthesias Among Community Members Exposed to the World Trade Center Disaster. Journal of occupational and environmental medicine. 2017 April;59(4):389-396. PubMed PMID: 28157767; PubMed Central PMCID: PMC5374747; DOI: 10.1097/JOM.0000000000000966.
N/A: Not NIH Funded	Thawani S, Wang B, Shao Y, Reibman J, Marmor M. Time to Onset of Paresthesia Among Community Members Exposed to the World Trade Center Disaster. International journal of environmental research and public health. 2019 April 22;16(8). PubMed PMID: 31013580; PubMed Central PMCID: PMC6518362; DOI: 10.3390/ijerph16081429.

C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

Nothing to report

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Have inventions, patent applications and/or licenses resulted from the award during the reporting period? No

If yes, has this information been previously provided to the PHS or to the official responsible for patent matters at the grantee organization?

C.5 OTHER PRODUCTS AND RESOURCE SHARING

Nothing to report

D. OVERALL PARTICIPANTS

D.1 WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

Commons ID	S/K	Name	Degree(s)	Role	Cal	Aca	Sum	Foreign Org	Country	SS
MARMOM01	Y	MARMOR, MICHAEL	MA,PHD	PD/PI	2.0	0.0	0.0			NA
	N	Vidal, Maria		Project Coordinator	6.0	0.0	0.0			NA
	N	Wang, Bin		Graduate Student (research assistant)	3.0	0.0	0.0			NA
	N	Zhang, JinChun		Graduate Student (research assistant)	2.0	0.0	0.0			NA
	Y	Thawani, Sujata		Co-Investigator	1.0	0.0	0.0			NA
SHAOY01	Y	Shao, Yongzhao	PHD	Co-Investigator	1.0	0.0	0.0			NA

Glossary of acronyms:
S/K - Senior/Key
DOB - Date of Birth
Cal - Person Months (Calendar)
Aca - Person Months (Academic)
Sum - Person Months (Summer)
Foreign Org - Foreign Organization Affiliation
SS - Supplement Support
RE - Reentry Supplement
DI - Diversity Supplement
OT - Other
NA - Not Applicable

D.2 PERSONNEL UPDATES

D.2.a Level of Effort

Not Applicable

D.2.b New Senior/Key Personnel

Not Applicable

D.2.c Changes in Other Support

Not Applicable

D.2.d New Other Significant Contributors

Not Applicable

D.2.e Multi-PI (MPI) Leadership Plan

Not Applicable

E. OVERALL IMPACT

E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES?

Not Applicable

E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE?

NOTHING TO REPORT

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

Not Applicable

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?

NOTHING TO REPORT

G. OVERALL SPECIAL REPORTING REQUIREMENTS

G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT REPORTING REQUIREMENTS

NOTHING TO REPORT

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

G.4.a Does the project involve human subjects?

Not Applicable

G.4.b Inclusion Enrollment Data

File(s) uploaded:
CumulativeEnrollmentReport_08NOV2019.pdf

G.4.c ClinicalTrials.gov

Does this project include one or more applicable clinical trials that must be registered in ClinicalTrials.gov under FDAAA?

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

Not Applicable

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT

No foreign component

G.10 ESTIMATED UNOBLIGATED BALANCE

Not Applicable

G.11 PROGRAM INCOME

Not Applicable

G.12 F&A COSTS

Not Applicable

Cumulative Inclusion Enrollment Report

This report format should NOT be used for collecting data from study participants.

Study Title: World Trade Center Exposures, Neuropathic Symptoms and Nervous System Injury

Comments:

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	1	16		1	1					**19**
Asian	4				1					**5**
Native Hawaiian or Other Pacific Islander										**0**
Black or African American	18	8			2					**28**
White	22			5						**27**
More Than One Race		1		8	2			1		**12**
Unknown or Not Reported	1	1		3	3					**8**
Total	**46**	**26**	**0**	**17**	**9**	**0**	**0**	**1**	**0**	**99**

I. OVERALL OUTCOMES

I.1 What were the outcomes of the award?

Paresthesias, or symptoms of tingling or numbness in the lower extremities (feet or legs) or upper extremities (hands or arms) have been reported by persons exposed to the World Trade Center disaster of September 11, 2019 ("9/11"), including members of the general community (local workers, residents, clean-up workers and passersby) and first-responders. This project explored the association of paresthesia with WTC exposure. As paresthesias are "symptoms," or self-reports of patients, another goal was to investigate whether "signs" of neuropathy (i.e., objective laboratory tests or clinical examinations) also were increased among those reporting paresthesia. A third goal was to investigate whether the reported paresthesias might be explained by non-WTC conditions or exposures, such as metabolic, infectious, or nutritional disorders, toxic exposures, carpal tunnel syndrome, or anxiety, which can lead to hyperventilation that in turn can cause paresthesia.

To address these issues, we analyzed data from community members enrolled in the Bellevue Hospital WTC Environmental Health Center. More than half of the 3,141 patients whose data we analyzed reported paresthesias at the time of enrollment in the WTC EHC seven to 15 years after 9/11. Our statistical analyses showed that paresthesia was independently and significantly associated with severity of exposure to WTC dust on 9/11, and working in a job requiring cleaning of WTC dust after 9/11. Paresthesia also was associated with decreased lung function and respiratory symptoms, which themselves may have been surrogates for intensity of WTC exposure.

In a second analysis of data from the WTC EHC patients, we used Cox regression analysis to investigate both the occurrence of paresthesia and the time-to-onset of paresthesia after 9/11 using both enrollment and monitoring (recall) data. Significant associations of time-to-onset of paresthesia again were found with severity of exposure to WTC dust on 9/11, and working in a job requiring cleaning of WTC dust after 9/11.

In a third study, we used a case-control design to investigate whether the symptom of paresthesia of the lower extremities was associated with objective signs of neuropathy. The study compared 41 cases (individuals from the WTC EHC with frequent paresthesia) to 38 clinic controls (WTC EHC patients who did not report paresthesias) and 20 community controls (healthy volunteers not enrolled in the WTC EHC, without exposure to the WTC disaster, and enlisted without consideration of paresthesia). We found that scores on the Norfolk Diabetic Neuropathy Quality of Life, the Utah Early Neuropathy Scale, the Michigan Neuropathy Screening Instrument, and a standardized neurological history and examination were significantly higher (worse) in cases than controls. Intraepidermal or sweat gland nerve fiber densities, which measure small nerve fiber disease, were abnormally low in 57% of cases, a significantly greater prevalence of abnormality than expected. Nerve conduction velocities were abnormally low in 3% of cases, which was not significantly different from expected. Neurologic abnormalities were uncommon among the community controls. Blood tests furthermore indicated that paresthesia cases did not have increased prevalences of other, non-WTC-related possible causes of paresthesia or peripheral neuropathy, such as diabetes or vitamin deficiencies. The data thus suggest that the paresthesias of the lower extremities reported by WTC survivors were not psychosomatic. The data are consistent with the hypothesis that WTC exposure was a risk factor for peripheral neuropathy. The data do not support alternative, non-WTC explanations for the reported paresthesias.