

Principal Investigator/Program Director (Last, First, Middle): Schwartz, Brian S., M.D., M.S.

DESCRIPTION: State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Describe concisely the research design and methods for achieving these goals. Avoid summaries of past accomplishments and the use of the first person. This abstract is meant to serve as a succinct and accurate description of the proposed work when separated from the application. If the application is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information. **DO NOT EXCEED THE SPACE PROVIDED.**

This competitive renewal application (Phase III) aims to address new fundamental questions regarding neurotoxicants, aging, and structure and function relations in the brain. Over the past ten years, a consistent body of evidence suggests that lead causes important changes in the adult brain. This research aims to understand how a neurotoxicant causes persistent or progressive structural change in the CNS, the relation of structural change to progressive functional loss, and insight on mediating factors (genetic polymorphisms, vascular health). In Phase II, 656 MRIs of the brain were obtained, volumes of 96 regions of interest (ROIs) were derived, and images were graded for white matter (WM) lesions using a standard method. In cross-sectional analysis, these observations were made: inverse associations between tibia lead and CNS volumes; direct associations between tibia lead and prevalence and severity of WM lesions; and direct associations between CNS volumes and neurobehavioral test scores (smaller volume, worse performance). The data now suggest that lead causes progressive functional decline in the adult CNS, and structural changes that are at least persistent, both beyond what is due to normal aging alone. To understand the progressive functional loss, research must investigate whether the structural lesion is persistent or progressive, whether WM and GM effects are linked, and whether there are genetic or vascular moderators of these effects. Funding is now sought to complete a second MRI on 500 subjects, another neurobehavioral assessment, and an evaluation of vascular health. The goals are to determine if tibia lead causes a persistent or a progressive structural lesion in the brain; if lead is a moderator of the effect of aging on CNS structure and function; how lead causes WM lesions using better WM imaging methods; how WM lesions, changes in GM volumes, and changes in function are related; and if vascular health is a mediator or moderator of lead and CNS injury and of structure and function relations.

PERFORMANCE SITE(S) (organization, city, state)

Johns Hopkins University, Bloomberg School of Public Health (BSPH), Baltimore, MD  
Johns Hopkins University, School of Medicine (SOM), Baltimore, MD  
University of Pennsylvania School of Medicine, Philadelphia, PA  
Geisinger Health System, Danville, PA

KEY PERSONNEL. See instructions. Use continuation pages as needed to provide the required information in the format shown below. Start with Principal Investigator. List all other key personnel in alphabetical order, last name first.

Name	Organization	Role on Project
Schwartz, Brian S., MD, MS	Johns Hopkins BSPH	Principal investigator
Bolla, Karen I., PhD	Johns Hopkins SOM	Co-investigator
Stewart, Walter F., PhD	Geisinger Health System	Co-investigator
Davatzikos, Christos, PhD	University of Pennsylvania	Co-investigator
Bandeen, Karen, PhD	Johns Hopkins BSPH	Co-investigator
Yousem, David M., MD	Johns Hopkins SOM	Co-investigator
Caffo, Brian, PhD	Johns Hopkins BSPH	Co-investigator

**Disclosure Permission Statement.** Applicable to SBIR/STTR Only. See instructions.  Yes  No