

STATEMENT OF WORK (SOW)

GENERAL INFORMATION

Title of Project:

Early Markers of Alzheimer's Disease (AD) in Baltimore Longitudinal Study of Aging (BLSA) Participants - Structural and Functional Brain Changes: Quantitative Analysis of Longitudinal MR Images

Statement of Need and Purpose:

The National Institute on Aging (NIA) requires specialized, non-commercial services to process and quantify magnetic resonance (MR) images from the Baltimore Longitudinal Study of Aging (BLSA). The contractor shall apply established image analysis methods to Government-provided datasets and deliver consistent quantitative measures and supporting image files. This requirement covers processing and analysis services; it does not require the development, validation, or delivery of new software or algorithms.

The BLSA is an ongoing longitudinal study of aging. NIA has collected brain images from participants since 1994 and uses quantitative measures of brain structure and function to examine changes associated with normal aging, cognitive change, and Alzheimer's disease. Analysis under this contract must account for visits acquired over time and changes in scanner or acquisition protocol so that the resulting measures can be compared with historical BLSA data. NIA conducts its own analyses of positron emission tomography (PET) data; this contract supplies anatomical labels and registration information for that work.

Background Information and Objective:

Since 1958, the Baltimore Longitudinal Study of Aging (BLSA) has been a major research program conducted by the National Institute on Aging (NIA). The BLSA is a multi-disciplinary study of physiologic and psychological aspects of normal aging in community-dwelling men and women. Active BLSA participants are volunteers who visit the Clinical Unit of the NIA-Intramural Research Program (IRP) in Baltimore, MD for testing every 1 to 4 years. Since 1994, the NIA has been conducting a longitudinal brain imaging study of older adults in the BLSA to characterize individual differences in longitudinal brain changes, to investigate the extent to which these brain changes underlie individual differences in cognitive aging, to identify brain changes that may be predictors of cognitive decline and Alzheimer's disease, and to assess the impact of potential modulators of brain and cognitive aging. As of October, 2024, more than 4000 neuroimaging evaluations have been performed for BLSA participants. As part of this research program, it has also been necessary to develop and validate sophisticated tools for analysis of longitudinal neuroimaging data that can be applied in large-scale studies. Thus, this project has involved the development, validation, and refinement of novel image analysis tools and the application of these tools to longitudinal Magnetic Resonance (MR) imaging scans and Positron Emission Tomography (PET) measures of regional cerebral blood flow, amyloid and tau deposition in brain. More recently, these tools include advanced machine learning approaches using pattern analysis to classify clinical status and aging trajectories of individuals based on structural and functional brain images.

The work of this requirement will continue to focus on the application of sophisticated tools and quantitative analysis of longitudinal MRI data acquired from BLSA participants. Thus, the proposed contract will apply methods developed in prior acquisitions, that allow continuity of research and provide longitudinal consistency of measures of global and regional brain volumes and ischemic lesion volumes, as well as functional MR data, including consistency with MR data acquired during earlier phases of this project (since 1994). This Contract will also require the application of sophisticated analytic approaches, including previously developed machine learning and pattern analysis methods, to allow classification of risk for cognitive impairment and likelihood of maintenance of cognitive resilience on an individual subject basis.

The principal goal of this procurement is to provide quantification of MR imaging scans to provide measures of brain structure and function in BLSA participants, including heterogeneous brain aging trajectories. Specifically, these data will allow NIA investigators to continue to address the following questions:

What are the rates and regional distribution of changes in brain anatomy in non-demented men and women throughout adulthood?

What is the frequency and progression of brain abnormalities in older adults and what is the clinical significance of these findings for cognitive aging?

Against a background of age-related changes in brain structure, which changes predict cognitive impairment and Alzheimer's disease, and conversely, what are the predictors of the maintenance of cognitive health or cognitive resilience?

What factors modulate cognitive and brain aging and how do they impact brain-behavior associations?

SCOPE OF WORK

General Requirements:

Independently and not as an agent of the Government, the Contractor shall furnish all the necessary services, qualified personnel, material, equipment, and facilities, not otherwise provided by the Government as needed to perform the Statement of Work below:

General Requirement: The Contractor shall be responsible for image processing and quantitation of 300 newly acquired MR datasets. The image processing must be consistent with methods used in earlier phases of the BLSA neuroimaging study to allow longitudinal consistency of data analysis and continuity of research. NIA will also supply existing reference datasets needed for longitudinal comparison.

Specific Requirements:

The purpose of acquiring structural MR images is twofold - to provide information on regional brain structure and function and to localize regions of interest for the quantitation of PET studies. (Analysis of PET scan data is performed in the NIA Laboratory of Behavioral Neuroscience (LBN)). Therefore, image analysis must be conducted using tools developed during the previous acquisition and include the following: differentiation and quantification of brain volumes and cerebrospinal fluid (CSF),

differentiation and quantification of gray and white matter volumes, definition and quantification of cortical and subcortical regions, quantification of lesion volumes, including infarcts and periventricular hyperintensities, labeled templates of brain regions for registration and overlay on PET images for regional definition. In addition, the Contractor shall provide RAVENS (regional analysis of volumes examined in normalized space) images for gray matter, white matter, and cerebrospinal fluid. In addition to continued analysis of regional brain measures, the following measures during the previous acquisitions will be highlighted.

1: Compute machine learning-derived scores based on existing algorithms, including "SPARE-AD", "SPARE-BA" and "R" atrophy indices, for all new and existing MR images. In addition, apply to BLSA MR images more recent indices that use multi-modal imaging data to allow investigation of heterogeneous patterns of brain aging, as well as the factors underlying this variation. For example, these new indices may include features extracted from structural MRI, diffusion MRI, and resting state functional MRI to capture brain patterns of AD, aging, as well as different dimensions of brain aging trajectories.

2: Apply previously developed image harmonization methods for analysis of longitudinal images over time. Based on the approaches developed in prior acquisitions, deep learning methods will be used to address the challenges of BLSA scanner changes. These methods utilize extensive enrichment of a training set by models of contrast and resolution change, followed by robust deep learning training, providing methods that are robust to scanner variations. These advancements shall be backwards and forward compatible with BLSA acquisition protocols.

3. The Contractor shall provide analysis of validation data acquired by NIA investigators during scanner changes, typically involving 10-20 image datasets.

Specific Requirements:

- Quantitative Image Analysis

The BLSA neuroimaging study requires stable and reliable approaches to analysis that account for the longitudinal nature of the BLSA MR imaging data. Methods that maximize the consistency and accuracy of longitudinal data across scanners and over time are required. Multi-atlas approaches as currently implemented in the MUSE software suite (or equivalent) shall be applied to obtain accurate estimates of very subtle longitudinal changes during normal aging and accelerated changes associated with cognitive impairment.² Of particular importance is the modeling of abrupt changes in imaging contrast and noise introduced by scanner or protocol changes, requiring image harmonization approaches. The Contractor shall provide both estimates of global and regional tissue volumes, as well as images for voxel-wise analysis.

- Machine learning derived indices of brain atrophy patterns.

This contract requires continued application of indices reflecting dimensions of age- and neurodegenerative disease related brain atrophy for investigation of heterogeneous patterns of brain aging. Examples of the approach used previously in the BLSA include the SPARE-AD³ (or equivalent) and

SPARE-BA⁴ (or equivalent) approaches, as well as more dimensions of brain atrophy as described in recent publications.⁵

- Data Security.

The Contractor shall provide a data security plan to ensure the confidentiality of participant information and the integrity of all data collected under this contract, consistent with standard commercial data-handling practices and applicable federal data security requirements (e.g., FISMA/FedRAMP-aligned controls, as applicable).

- Replication, Dissemination or Use of Results.

All data and images generated under this contract are the property of the National Institutes of Health (NIH). NIH will have rights to use outputs generated by the Contractor's software for this project (the Contractor retains ownership of its underlying proprietary software and methodology).

PERIOD OF PERFORMANCE

The anticipated period of performance is November 16, 2026 to November 15, 2027.

CONTRACT TYPE AND PRICING

This Statement of Work is firm fixed price. The Contractor shall perform the services and provide the deliverables described in this Statement of Work for a firm fixed price. This price includes all labor, materials, travel, expenses, overhead, and profit required to complete the work.

The total price will not change based on the Contractor's actual costs. Any change to the scope, deliverables, schedule, or price must be documented in a written contract modification approved by authorized representatives of both parties, subject to any applicable Changes clause in the contract.

GOVERNMENT RESPONSIBILITIES

The government will provide MR imaging data for 300 new MR datasets, along with any existing reference datasets necessary for longitudinal comparison.

DELIVERABLES

Deliverable	Frequency
Quantitative volumetric results (per scan, per region)	Every 6 months
Intermediate processing files (regional definitions, segmentations, coordinate maps, normalized volume maps)	Every 6 months
Spreadsheet of participant/visit identifiers, scan types, and quantitative measures (including composite atrophy scores)	Every 6 months
Labeled anatomical templates per scan	Every 6 months
Registration maps/transformation matrices for PET overlay	Every 6 months
Final report	Within 15 calendar days of end of period of performance

Final Report Contents:

- Cover page (contract number/title, period of performance, Contractor name/address, authors, submission date)
- Number of participants/scans processed
- Any issues encountered and corrective actions taken

PROJECT MANAGEMENT

Within two weeks of award, the Contractor shall submit a project plan describing its processing workflow and schedule, and shall designate a Project Manager/point of contact as the primary liaison with the NIA Contracting Officer's Representative (COR). The Contractor shall hold a teleconference meeting with the NIA COR to review the plan within one week of the submission of the project plan.

OTHER CONSIDERATIONS

Information System Security Plan:

The Contractor shall provide a data security plan to ensure the confidentiality of participant information and the integrity of all data and image processing under this contract.

Data Rights:

The contractor shall deliver the data, images, and processing outputs required by this SOW to NIA. The parties' rights in delivered data and any pre-existing contractor software or methodology are governed by the applicable contract clauses and any expressly negotiated license terms. Delivery of outputs does not itself transfer ownership of the contractor's pre-existing software.

Data will be used by members of the NIA to examine the relation between changes in brain structure and function with normal aging and changes in neuropsychological performance. All data and image processing under this contract shall be forwarded to the NIA and a copy will be stored at the NIA.

Results will be disseminated to the scientific community via presentations at scientific meetings and publications in professional journals. Collaboration of the Contractor principal and co-principal investigators with NIA Investigators in data analyses and reporting of study results will be encouraged.

Section 508—Electronic and Information Technology Standards:

NA

Publications and Publicity:

NIA and its authorized collaborators may use the delivered outputs for research and reporting in accordance with the contract. The contractor shall not independently publish, present, or otherwise disclose BLSA data or results obtained under this contract without prior written NIA approval. Any authorized abstract or publication involving BLSA data is subject to applicable NIH clearance procedures.

Confidentiality of Information:

Participant information is protected under the Privacy Act and, where applicable, a Certificate of Confidentiality. The Contractor shall handle all participant data in accordance with these protections and its data security plan.

References:

1. Doshi J, Erus G, Ou Y, Resnick SM, Gur RC, Gur RE, Satterthwaite TD, Furth S, Davatzikos C; Alzheimer's Neuroimaging Initiative. MUSE: MULTI-atlas region Segmentation utilizing Ensembles of registration algorithms and parameters, and locally optimal atlas selection. *Neuroimage*. 2016 Feb 15; 127:186-95
2. Xue Z, Shen D, Davatzikos C. CLASSIC: consistent longitudinal alignment and segmentation for serial image computing. *Neuroimage* 2006;30 388-399.
3. Davatzikos C, Xu F, An Y, Fan Y, Resnick SM. Longitudinal progression of Alzheimer's-like patterns of atrophy in normal older adults: the SPARE-AD index. *Brain : a journal of neurology* 2009;132:2026-2035.
4. Habes M, Pomponio R, Shou H, Doshi J, Mamourian E, Erus G, Nasrallah I, Launer LJ, Rashid T, Bilgel M, Fan Y, Toledo JB, Yaffe K, Sotiras A, Srinivasan D, Espeland M, Masters C, Maruff P, Fripp J, Völzke H, Johnson SC, Morris JC, Albert MS, Miller MI, Bryan RN, Grabe HJ, Resnick SM, Wolk DA, Davatzikos C; iSTAGING consortium, the Preclinical AD consortium, the ADNI, and the CARDIA studies. The Brain Chart of Aging: Machine-learning analytics reveals links between brain aging, white matter disease, amyloid burden, and cognition in the iSTAGING consortium of 10,216 harmonized MR scans. *Alzheimers Dement*. 2021 Jan;17(1):89-102.
5. Yang Z, Wen J, Erus G, Govindarajan ST, Melhem R, Mamourian E, Cui Y, Srinivasan D, Abdulkadir A, Parmpi P, Wittfeld K, Grabe HJ, Bülow R, Frenzel S, Tosun D, Bilgel M, An Y, Yi D, Marcus DS, LaMontagne P, Benzinger TLS, Heckbert SR, Austin TR, Waldstein SR, Evans MK, Zonderman AB, Launer LJ, Sotiras A, Espeland MA, Masters CL, Maruff P, Fripp J, Toga A, O'Bryant S, Chakravarty MM, Villeneuve S, Johnson SC, Morris JC, Albert MS, Yaffe K, Völzke H, Ferrucci L, Bryan NR, Shinohara RT, Fan Y, Habes M, Lalouis PA, Koutsouleris N, Wolk DA, Resnick SM, Shou H, Nasrallah IM, Davatzikos C. Five dominant dimensions of brain aging are identified via deep learning: associations with clinical, lifestyle, and genetic measures. *Nature Medicine* 2024 Oct;30(10):3015-3026.