THE McKNIGHT BRAIN RESEARCH FOUNDATION
Preserving memory, enhancing life
McKNIGHT BRAIN INSTITUTES
UNIVERSITY OF ALABAMA AT BIRMINGHAM • UNIVERSITY OF ARIZONA • UNIVERSITY OF FLORIDA • UNIVERSITY OF MIAMI

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Department of Neurobiology

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April 17, 2024

Dear McKnight Brain Aging Registry Trustees,

This memo is in response to the MBRF trustees' letter of October 30, 2023 requesting a single collaborative proposal outlining how remaining funds from the McKnight Brain Aging Registry will be used. The amount described in that letter was $88,519.11. The aim of our current proposal on the use of these funds is to enhance the impact of the McKnight Brain Aging Registry on the field. We will do this by making these data easier for researchers to use, including use to support externally funded grant proposals.

Overarching goal: To distribute workable/easy to analyze versions of datasets from the MBAR to users who will use it for 1) analysis to create impactful peer-reviewed research papers, 2) preliminary data for future grant proposals. These datasets have been instrumental for several current projects across the MBRF Institutes and have the potential to launch further projects. In service of these goals, we propose here a limited-in-scope approach to create the following 8 deliverables, which will together enhance the impact of the McKnight Brain Aging Registry.

1. An organized, efficient, and PHI-friendly method for getting raw data for analysis to McKnight investigators.

- We will create a simple method for data transfer that will allow data for potential future studies to be transferred from our centralized data storage to various MBRF-affiliated labs, as facilitated by a data curator. This will involve sharing the data through a secure file sharing platform, Box. This method requires significant time and effort to curate data for each investigator. Approved requests will be forwarded to Paul Stewart, our data curator, who is employed at UAB under the direct supervision of Dr. Kristina Visscher, associate MBI director at UAB. Paul Stewart will confirm the correct datasets and share appropriate datasets with investigators (for example, information about participant ages that are over 89 are converted to "89+" for investigators not included in the IRB approval, in accordance with protected health information guidelines). Paul Stewart has been working in a similar capacity with the NIH-funded Human Connectome Project, Connectomes in Human Diseases subproject run through Dr. Visscher's lab at UAB (the Macular Degeneration and Plasticity Project). The remainder of Paul Stewart's full-time work will be spent doing similar work with other NIH-funded grants in Dr. Visscher's lab.

- Requests for access to blood will be coordinated with investigators at University of Florida. They will thaw and aliquot blood biomarkers as needed for further analyses done by other investigators. The current budget does not cover the processing of

blood biomarkers, thus that processing (which is often costly) will be done by interested investigators who have obtained independent funding to work with the blood provided by this project.

- We will send emails quarterly to all members of the four McKnight sites, reminding them of the availability of these datasets. These emails will include links to our researcher-facing website (see item 3). This website will, among other things, detail the procedure for obtaining datasets. This involves filling out a Data Access Form (including details about the data requested and information about a power analysis about the question being addressed in the proposed analysis). This form will be collated by the data curator and assessed by the McKnight Brain Aging Registry Scientific Advisory Committee which meets monthly.

2. Generation of minimally preprocessed data from our datasets, as well as generation of selected early analyses

While sophisticated users of data frequently want to start their analyses with raw datasets to apply the tools most appropriate for their exact research question, a dataset like the MBAR involves a wide range of different types of datasets which many investigators may not have sufficient expertise to process. For this reason, we will make several levels of processed data available. This approach will decrease the effort and time required by researchers to analyze these datasets accurately.

Data made available to users will be categorized as:

- **Raw data**: after basic quality control and checking, as obtained from participants. These raw data include:
    - Pdfs of in-person behavioral measures
    - Raw MRI datasets
    - Blood; frozen blood samples. (These are limited in quantity)
    - Trial-level scores on individual behavioral and neuropsychological tests
- **Minimally processed biomarker data**: results from processing on frozen blood samples. For example, raw results of ELIZA.
- **Minimally preprocessed MRI data**: this involves applying a set of standard preprocessing algorithms to the data, to prepare for a set of typical data analyses. For example, skull stripping, identification of white matter and pial boundaries, identification of timepoints of movement in functional MRI, etc. (see Glasser et al., 2016).
- **Processed images**: whole brain image files; one per participant, obtained after data processing. For example, individual participants' whole brain functional connectivity to the posterior cingulate cortex.
- **Tabular data**: This involves data that has been processed to give a single value for each participant. These data include, for example:
    - Participant demographics
    - Behavioral data factor scores indicating weighting on each of 5 factors (see Nolin et al., 2022)
    - Categorization of participants based on exercise levels (sedentary vs cardio and strength training, see Ho et al., 2024)
    - FMRI data indicating strength of connection among brain regions designated as the "Default Mode Network"

- Cortical thickness of each of >200 pre-defined brain regions
- Levels of BDNF measured in blood
- Data that are potentially identifiable (e.g., age over 89 years old) will be distributed only to investigators who are on the IRB for this project.

3. A researcher-facing website that shows exactly what data exists from our datasets and documents indicating how to go about accessing this data

- It will be instrumental to create a website that describes in detail the contents of the MBAR dataset. Any researcher interested in using the data will then have a full, detailed description of both the data which can be available to them. This includes a detailed list of demographic and behavioral data that will be available for each participant. In addition, the dataset includes data of several categories (as described above in item 2). The categories of data will be described in a clear way on the website. Researchers who are interested in the data will be able to see detailed descriptions of how each scan and behavioral measure was collected, and any relevant technical parameters that could help them determine whether this dataset will be appropriate for their research. This will represent Phase 1 of the website. Phase 2 (see item 7, below) will incorporate components for the lay-public. Development of Phase 1 of the website involves careful documentation of the full dataset, which will be a summer project in year 1 for Hannah Cowart, who worked on the MBAR project while an undergraduate, and who has a strong understanding of the details of data acquisition.

4. A paper that documents these datasets and their potential, published in a reputable journal

- The MBAR scientific advisory committee will publish a paper describing our dataset in a high impact-factor open-access journal, for instance *Nature Scientific Data*. This will provide further understanding of the dataset and its significance and generate interest in the dataset. The budget includes support to pay the Article Processing Charge (APC) necessary to publish our dataset in *Nature Scientific Data* (https://www.nature.com/sdata/) or another similar journal. Our code related to preprocessing will also be made available on GitHub.

5. Development of a more streamlined and sustainable method for dissemination of data.

- We will explore the sustainability and feasibility of making these datasets available to the public via currently NIH and NSF-funded data sharing platforms. For example, openNeuro https://openneuro.org/ allows uploads of both MRI data and supported behavioral data types. The benefits of such sharing approaches include sustainability, as many of them (including openNeuro) have been funded explicitly to act as a repository for the foreseeable long-term future, including extensive long-term maintenance costs. These data would be uploaded to the widely sharable platform only after 2 years' time available to the McKnight Brain Institute groups. This allows members of the McKnight consortium to have exclusive use of the datasets until this timeframe is complete and encourages McKnight Brain Institute members to publish their analyses using these datasets, but also encourages the widest-possible utility of the datasets. If for some reason

further examination of this technique finds that these sustainable methods are not feasible or optimal (for example, extensive understanding of the appropriate IRB and data use agreement information is needed), we will develop a different sustainable method for long-term use and dissemination of the data.

- After the completion of this two-year effort, the work to analyze and disseminate the MBAR data will be sustained through shared online platforms. A number of projects may use these datasets, but the work involved in those projects will be funded through separate proposals.

6. Quantification of the research products (papers/grants/etc.) that come from this effort.

- We will organize detailed information about the papers, grants, and any other work created with this dataset using an internal database. Additionally, any papers using this data will be listed on our public-facing website. An automated email will be sent by our data curator every 6 months until the end of the award period (2 years) to follow up with any users of the data, asking them for information about the status of any future or ongoing research involving the data. These results will be collated and published on our website. All users of the data during the duration of this award will agree to providing this information as a prerequisite to obtaining the datasets.

7. An extension to the website that explains to the lay public, trustees, and future researchers the history, outcomes, and future of the dataset; to be linked to the McKnight website.

- In phase 2 of the website development, the website will be extended to include the scientific rationale behind the collection of the dataset, history of the dataset, links to papers using the data, and outcomes. This portion of the website will be public-facing, giving easy to understand summaries of outcomes (as contrasted with phase 1 of the website, which includes researcher-facing information).

8. Updates to the shared dataset that include select analyses of datasets.

- As researchers produce more sophisticated analyses of these data and publish on them, such analytical products will be added to the database to be shared with other researchers. This will be done with consent of the researchers and only after publication of the data. Several high-impact journals require sharing of the data used in publication, so this should be useful to researchers. We anticipate, for example, having ‘brain age scores’ based on brain anatomy, dynamic functional connectivity metrics, or structural connectivity metrics available for each participant, after these have been calculated by our research partners. Future work could then relate these more complex products of analysis to other measures. Following approval from the researchers who published these data, the data curator will add these measures to the database and to the researcher-facing website, with links to the publication, so that the methods for deriving those values will be clearly understood by future researchers.

Timeline: The goals outlined in this document will be completed in 2 years.

- **Deliverables in year 1:** Method for disseminating data to McKnight researchers and documentation of data distribution for at least 8 new data analyses (item 1). Generation of minimally processed dataset (item 2). Phase 1 of website (item 3). Quantification of research products through website as well as through official emails to all McKnight sites (item 6).
- **Deliverables in year 2:** Paper publication documenting the dataset (item 4). Transition to sustainable method for making data accessible in perpetuity (item 5). Quantification of new research products through website as well as through official emails to all McKnight sites (item 6). Phase 2 of website, including public-facing information (item 7). Updates to datasets based on new analyses (item 8).
- **Total Budget for 2 years: $89,530. See breakdown in below Budget table.**

The McKnight Brain Aging Registry Scientific Advisory Committee is composed of investigators from each of the four institutes: Dr. Bonnie Levin and Dr. Tatjana Rundek from Miami, Dr. Ron Cohen and Dr. Adam Woods from University of Florida, Dr. Gene Alexander from University of Arizona, and Dr. Kristina Visscher from UAB. This group has met regularly since the inception of the McKnight Brain Aging Registry, and currently meets monthly to discuss and approve new proposals. They will continue to meet monthly for the duration of this 2-year award period.

The following pages outline the budget for this endeavor, the bibliography, as well as a list of projects being done with these data, and their current status.

Thank you for your past and continued support of this important endeavor. I look forward to your response. Please let me know if you have any questions.

Sincerely,

Signed by MBAR Scientific Advisory Committee members and McKnight Leadership Council members (see below)

Budget:

Principal Investigat	Kristina M. Visscher, Ph.D.												
Sponsor:	McKnight Brain Aging Registry distribution												
				Project Period I 7/1/24 6/30/25					Project Period II 7/1/25 6/30/26				
Personnel Name	Role on Project	Current Annual Salary	Frng.	Effort	Amount	Fringe	Total	Base Salary	Effort	Amount	Fringe	Total
Other Personnel												
Paul D Stewart	Researcher II	$ 55,000	35.2%	55%	$ 30,250	$ 10,648	$ 40,898	$ 60,000	20%	$ 12,000	$ 4,224	$ 16,224
Hannah Cowart	Researcher 1	$ 40,000	35.2%	10%	$ 4,000	$ 1,408	$ 5,408		0%	$ -	$ -	$ -
Subtotal Personnel					$ 34,250	$ 12,056	$ 46,306			$ 12,000	$ 4,224	$ 16,224
NON-PERSONNEL EXPENSES												
Equipment												
Travel				Travel					Travel			
Supplies				Supplies					Supplies			
Tuition				Tuition					Tuition			
Other Expenses:												
Website Development							$ 2,000					$ 2,000
thawing, aliquotting, and/or distribution of blood							$ 10,000					$ 10,000
Publication costs							$ -					$ 3,000
SUBTOTAL DIRECT COSTS							$ 58,306					$ 31,224
Indirect costs			0.0%				$ -					$ -
PROJECT TOTAL COSTS							$ 58,306					$ 31,224

Bibliography:

Glasser, M. F., Smith, S. M., Marcus, D. S., Andersson, J. L. R., Auerbach, E. J., Behrens, T. E. J., Coalson, T. S., Harms, M. P., Jenkinson, M., Moeller, S., Robinson, E. C., Sotiropoulos, S. N., Xu, J., Yacoub, E., Ugurbil, K., & Van Essen, D. C. (2016). The Human Connectome Project's neuroimaging approach. Nature Neuroscience, 19(9), 1175–1187. https://doi.org/10.1038/nn.4361

Ho BD, Gullett JM, Anton S, Franchetti MK, Bharadwaj PK, Raichlen DA, Alexander GE, Rundek T, Levin B, Visscher K, Woods AJ, Cohen RA. Associations between physical exercise type, fluid intelligence, executive function, and processing speed in the oldest-old (85 +). Geroscience. 2024 Feb;46(1):491-503. Doi: 10.1007/s11357-023-00885-4. Epub 2023 Jul 31. PMID: 37523033; PMCID: PMC10828155.

Nolin, S. A., Cowart, H., Merritt, S., McInerney, K., Bharadwaj, P. K., Franchetti, M. K., Raichlen, D. A., Jessup, C. J., Hishaw, G. A., Van Etten, E. J., Trouard, T. P., Geldmacher, D. S., Wadley, V. G., Porges, E. S., Woods, A. J., Cohen, R. A., Levin, B. E., Rundek, T., Alexander, G. E., & Visscher, K. M. (2022). Validity of the NIH toolbox cognitive battery in a healthy oldest-old 85+ sample. Journal of the International Neuropsychological Society, 1–10. https://doi.org/10.1017/S1355617722000443

Proposals and outcomes:

PI	Name of proposal	Status
Visscher/ Sims	Relationship of cognitive performance to brain network dynamics in the healthy oldest old	submitted for publication
Visscher/ Sims	Validity of the NIH Toolbox Cognitive Battery in Adults over 85	published
Cohen/Rohl	Relationship of Predicted Brain Age to Neurocognition	approved
Britton	Relationship of Time-Shifted BOLD Signal to Crystallized-Fluid Cognition Discrepancy and Predicted Brain Age	approved
Alperin	Cerebral Blood Flow in the oldest old: Gender differences, clinicaland neurocognitive correlates	approved
Gullett	White Matter Integrity Mediates Age-related Neuropsychological Performance in the Oldest Old	approved
Parpura/Caceres	Modeling Episodic Memory measures and Hippocampal measures in an Oldest-Old AdultCohort	submitted for publication
Langer/Cohen	Contributions of Resting State Functional Connectivity and Diffusion Tensor Imaging to Working Memory Performance	approved
Ho	Differences in Executive Functioning and Memory between Runners and Lifters	published
Jon B Williamson; Ro	between inflammation, cerebral blood flow, and vascular burden.	approved
Chen	Depression, Loneliness, Perceived Isolation, and Social Networking during COVID-19	approved
Levin	Successful living among the oldest old	approved
Alexander	Physical activity and brain aging	approved
Levin	Psychosocial adaptation among the oldest old during COVID	approved
Porges	GABA MRS in the context of successful brain aging	submitted for publication
Alperin and Cohen	blood flow in the oldest old, as measured with CINE-PC	approved

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