Concept Paper

Provisional Paper Title: Brain age as a Mid-life biomarker of unhealthy aging

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P.I. Sponsor: Terrie Moffitt, Ahmad Hariri
(if the proposing author is a student or colleague of an original PI)

Today's Date: 10/30/17

Please describe your proposal in 2-3 pages with sufficient detail for helpful review.

Objective of the study:

As the global populations ages, there will be a requisite increase in global health burden of aging related diseases[1]. Individuals vary substantially in the speed at which they age and in their susceptibility to aging related health decline[2]. Reliable measures of these individual differences in the rate of aging would allow better prediction of health outcomes as well as increased ability to identify individuals in most need of anti-aging intervention before irreversible decline has taken place[3]. Aging related deterioration of the brain is particularly detrimental to health and well-being because of the significant burden of cognitive decline and dementia[4].

Recent work has demonstrated that the chronological age of an individual's brain can be reliably predicted from magnetic resonance imaging (MRI) data[5]. Interestingly, differences between MRI-estimated brain ages and a person's true chronological age appear to be related to their risk for neurological dysfunction, including cognitive decline[6] and schizophrenia[6], their history of traumatic brain injury[7], and their future risk of death[8]. However, while several different brain-age metrics have been proposed, no study has yet investigated them together in the same group of humans. Of particular interest for development of brain-age measurements as clinical tools is whether MRI measures can serve as markers of biological aging of the brain in a relatively young population for whom prevention is still possible.

We propose investigating brain aging metrics in the Dunedin birth cohort. Using a birth cohort is important because chronological age is inherently controlled for. All variation in brain age will reflect biological aging of the brain. This 45-year-old cohort will also have limited aging related disease and therefore representative of a population for whom anti-aging intervention may be most effective. We would like to know if brain age measures are related to risk factors for neurodegeneration as well as cognitive decline in mid-age. We would also like to investigate the relationship between brain age and measures of biological aging derived from non-brain biomarker panels.

Data analysis methods:

Our analysis will address 3 questions:

1) **Do proposed measures of brain aging show variation in a birth cohort who are all the same chronological age and is such variation correlated across different brain aging measures?**

Analysis will compute distributions of different brain age measures and test correlations

between different measures. Previously developed predictive models of brain age have been based on different machine learning algorithms and used different types of brain imaging data as inputs but have yet to be tested in the same sample. We will compare 3 models leading models available at the time of writing this concept proposal[5,6,9].

2) **Is measured brain aging accelerated in individuals with epidemiological risk factors for neurodegeneration?**

   Analysis will use OLS regression to test associations between brain age and
   - **a.** Psychopathology (thought disorder)
   - **b.** Drugs (cannabis use)
   - **c.** TBI (use head injury records)
   - **d.** Hypertension
   - **e.** Diabetes and pre-diabetes
   - **f.** Genetic risk for schizophrenia
   - **g.** Genetic risk for Alzheimer's

3) **Is measured brain aging accelerated in individuals showing poor cognitive function and evidence of early-emerging cognitive decline?**

   Analysis will test associations between brain age and cognitive function at age 45. Analysis will also test associations with cognitive decline measured as changes from childhood through age 45 years. In addition, we will analyze associations between brain age and other neuropsychological measures that integrate cognitive function and physical functioning (Gait Rite and grooved pegboard).

4) **Is accelerated brain aging associated with faster aging of the body?**

   Analysis will test associations between brain age and measures of aging in the body (KDM biological age, pace of aging, age-related homeostatic dysregulation, epigenetic clocks and facial aging)

Variables needed at which ages:

P factor at age 45
Lifetime cannabis use (joint years or other metric)
Head injury records across lifetime
Hypertension across lifetime
PGS for schizophrenia
PGS for Alzheimer's
Biological aging variables (Pace of Aging, KDM Biological Age, Epigenetic Clocks, Telomeres, Facial Age)
Childhood IQ (average over 7, 9, 11, 13)
Adult IQ at 38 and 45
Gait Rite at age 45
Grooved pegboard at age 38

Significance of the Study (for theory, research methods or clinical practice):

The significance of this study is to extend our understanding of brain age as a clinical tool that may be useful in identifying individuals at midlife who are at risk for age-related health problems. This project will also provide a novel measure (brain age) to the Dunedin study that will be useful in future studies of midlife aging.

References cited:

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8. Cole JH, Ritchie SJ, Bastin ME, et al. Brain age predicts mortality. *Mol Psychiatry*. 2017;(February):1-8. doi:10.1038/mp.2017.62.
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Data Security Agreement

Provisional Paper Title	Brain age as a Mid-life biomarker of unhealthy aging
Proposing Author	Maxwell Elliott
Today's Date	10/27/17

Please keep one copy for your records and return one to the PI Sponsor

Please initial your agreement

ME	I am current on Human Subjects Training (CITI (www.citiprogram.org) or equivalent)
ME	My project is covered by Duke or Otago ethics committee OR I have /will obtain ethical approval from my home institution.
ME	I will treat all data as "restricted" and store in a secure fashion. My computer or laptop is: a) encrypted (recommended programs are FileVault2 for Macs, and Bitlocker for Windows machines) b) password-protected c) configured to lock-out after 15 minutes of inactivity AND d) has an antivirus client installed as well as being patched regularly.
ME	I will not "sync" the data to a mobile device.
ME	In the event that my laptop with data on it is lost, stolen or hacked, I will immediately contact Professor Moffitt or Caspi. (919-684-6758, tem11@duke.edu, ac115@duke.edu)
ME	I will not share the data with anyone, including my students or other collaborators not specifically listed on this concept paper.
ME	I will not post data online or submit the data file to a journal for them to post. *Some journals are now requesting the data file as part of the manuscript submission process. The Dunedin Study Members have not given informed consent for unrestricted open access, so we have a managed-access process. Speak to Terrie or Avshalom for strategies for achieving compliance with data-sharing policies of journals.*
ME	I will delete all data files from my computer after the project is complete. Collaborators and trainees may not take a data file away from the office. The data remains the property of the Study and cannot be used for further analyses without an approved concept paper for new analyses.

Signature: 

CONCEPT PAPER RESPONSE FORM

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Provisional Paper Title	Brain age as a Mid-life biomarker of unhealthy aging
Proposing Author	Maxwell Elliott
Other Contributors, in alphabet order	Dan Belsky, Avshalom Caspi, Ahmad Hariri, David Ireland, Annchen Knodt, Terrie Moffitt, Richie Poulton
Potential Journals	
Today's Date	10/30/17
Intended Submission Date	When imaging data collection is completed, approximately Jan 2019

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B. To be completed by potential co-authors:

	Approved
	Not Approved
	Let's discuss, I have concerns

Comments:

Please check your contribution(s) for authorship:

	Conceptualizing and designing the longitudinal study
	Conceptualizing and collecting one or more variables
	Data collection
	Conceptualizing and designing this specific paper project
	Statistical analyses
	Writing
	Reviewing manuscript drafts
	Final approval before submission for publication
	Acknowledgment only, I will not be a co-author

Signature:

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