Dunedin Study Concept Paper Template 2019

Provisional Paper Title: Individual differences in accelerated pace of biological aging: Science and policy implications

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

Today's Date: July 27, 2019

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

Objective of the study:

The aim of this report is to introduce the measurement of the Pace of Aging in the Dunedin Study, from age 26 to age 45, to validate the measure against measures of age-related deficits, and to examine the association between accelerated biological aging and brain functioning. Specifically, our objectives are:

To describe the measurement of the Pace of Aging from age 26 to age 45 years, and to document the magnitude of individual differences therein.

To validate the measure of the Pace of Aging against measures of facial aging, physical function, sensory function (hearing and vision), sexual function, and attitudes toward aging.

To test the association between Pace of Aging and cognitive function at age 45 and in relation to cognitive decline (from childhood to age 45).

To conduct a hypothesis free analysis of the brain correlates of accelerated aging.

Data analysis methods:

We will describe the measurement of the Pace of Aging. This will involve the repeated assessments of a panel of 19 biomarkers taken at ages 26, 32, 38, and 45 years. The 19 biomarkers are: body mass index, waist-hip ratio, glycated hemoglobin (HbA1C), leptin, blood pressure (mean arterial pressure), cardiorespiratory fitness (VO_2Max), forced expiratory volume in one second (FEV_1), forced vital capacity ratio (FEV_1/FVC), total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, apolipoprotein B100/A1 ratio, lipoprotein(a), creatinine clearance, urea nitrogen, C-reactive protein, white blood cell count, gum health, and caries-affected tooth surfaces. Change over time in each biomarker will be modeled with mixed-effects growth models, and these rates of change will be combined into a single index scaled in years of physiological change occurring per one chronological year. This is the main measure of the manuscript, around which we will report correlates.

Associations with the correlates of Pace of Aging (listed below will be conducted using OLS regression, sex adjusted. All distributions will be checked in advance, and where necessary, variables may be transformed to approximate normality.

Primary structural MRI analyses will follow the same framework. In the MRI "secondary" analyses, in which regional specificity is tested, correction for multiple comparisons will be performed using a false discovery rate correction across all regional measures.

Functional MRI associations while be investigated with General Functional Connectivity. An exploratory data-driven search for GFC correlates of the Pace of Aging will be performed with a Connectome Wide Association Study.

Variables needed at which ages:

Pace of Aging, age 26-45.

Correlates from age 45.

Facial aging. Rated by independent panel.

Physical functioning. We will use (physical limitations (SF36), handgrip strength, one-legged balance, visual-motor coordination, chair-stand test, step-in-place test, gait (all three walks).

Sensory 1. Vision. We will examine contrast sensitivity.

Sensory 2. Auditory: We will use Pure Tone Audiometry and Listening to Sentences in Spatialized Noise (LiSN-S).

Sexual dysfunction. Questions from the Sexual Relationships & Function component of the Reproductive Health interview: lacked interest, lacked enjoyment, performance anxiety, inorgasmic, not aroused, premature climax, painful intercourse, difficulty maintaining erection, vaginal dryness. Final measure will be determined on the basis of frequencies.

Interviewer rating of vitality and informant report of youthfulness. Use of these items will be determined on the basis of frequencies.

Attitudes toward aging.

Cognitive functioning. At age 45, the WAIS-IV generates the overall full-scale IQ, and in addition, four WAIS-IV indexes assess abilities that make up the IQ: Processing Speed, Working Memory, Perceptual Reasoning, and Verbal Comprehension. In addition, we will assess cognitive change from childhood to midlife.

Informant reports of cognitive difficulties.

Brain Structure at age 45

- Grey matter measures
    - Cortical thickness – whole brain (primary) and regional (secondary)
    - Surface area – Whole brain (primary) and regional (secondary)
    - Subcortical volume – hippocampus (primary) all other (secondary)
- White matter measures
    - Fractional Anisotropy – average FA (primary) and by tract (secondary)
    - White matter hyperintensity volume (primary)

Brain Function at age 45

- General Functional Connectivity (secondary)

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

The significance is threefold.

First, to introduce/extend the measurement of individual differences in the pace of biological aging.

Second, to validate the measurement of biological aging against standard tests that are used in geriatric settings (e.g., gait) and against measures with

ecological validity (e.g., facial aging).

Third, to test the link between physiological aging and aging of the brain, using both tests of neuropsychological functions and brain imaging.

The overarching message of the paper will be that aging is a 'justice issue.' Same-aged individuals age at vastly different rates. If our hypothesis is confirmed, it will document that individual differences in the pace of biological aging have consequences for individual and societal well-being. Social systems and practices that are age-graded (e.g., retirement, age-related benefits and entitlements, senior discounts, insurance policies) may be misguided and unfair—both to slow agers and fast agers--given the enormous variability in biological aging.

Data Security Agreement

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

Please initial your agreement: (customize as necessary)

x	I am current on Human Subjects Training [CITI www.citigrogram.org] or equivalent.
x	My project is covered by the Dunedin Study's ethics approval OR I have /will obtain ethical approval from my home institution (please specify).
	I will treat all data as "restricted" and store in a secure fashion. My computer or laptop is: • encrypted (recommended programs are FileVault2 for Macs, and Bitlocker for Windows machines) • password-protected • configured to lock-out after 15 minutes of inactivity AND • has an antivirus client installed as well as being patched regularly.
x	I will not "sync" the data to a mobile device.
x	In the event that my laptop with data on it is lost, stolen or hacked, I will immediately contact my PI Sponsor or Study Director
x	I will not share the data with anyone, including my students or other collaborators not specifically listed on this concept paper.
x	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 your PI Sponsor or Richie Poulton for strategies for achieving compliance with data-sharing policies of journals.*
x	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: _____Max Elliott, Renate Houts, Avshalom Caspi, Temi Moffitt