GROWUPGROWOLD
HUMAN DEVELOPMENT, BIRTH TO DEATH

Moffitt & Caspi
Genes Environment Health Behavior

**Concept Paper Form**

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| **Provisional Paper Title:** Association of age 3 brain health with age 45 physical function |
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| **P.I. Sponsor:** Terrie Moffitt, Avshalom Caspi<br>(if the proposing author is a student or colleague of an original PI) |
| **Today's Date:** Click here to enter date |

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

**Objective of the study:**

A paradigm shift has occurred in the aging literature. Historically, gerontologists have sought to cure specific, age-associated diseases (e.g., Alzheimer's disease, Parkinson's disease, cardiovascular diseases). This "whack-a-mole" approach (coined in part due to its inefficiency) is being replaced by the *geroscience perspective*, which seeks to understand biological aging holistically, treating aging itself as the disease process (Kennedy et al., 2014). With this reconceptualization of aging, we can further reconsider how the aging process fits alongside development in the lifespan. The *early-systems integrity perspective* states that individual variability in cognitive and physical health is present from the beginning of life, and is consistent and persistent across the lifespan, predicting aging outcomes (Deary, 2012). Taken together, these frameworks lay the foundation for investigations which connect early childhood to aging in mid- or late-life, creating many entry points for efforts to slow aging and prevent disease. Importantly, aging researchers should look beyond only studying older adults; we should consider insights that can be uncovered from younger populations. The Dunedin study provides a unique opportunity for these investigations because it is among very few datasets containing information from early childhood and later life.

Under the early-systems integrity framework, we propose an investigation about the relationship between brain health at age 3 and physical function at age 45. Previous research has shown that frailty tests traditionally used in geriatrics (e.g., gait speed) are associated with central nervous system function (Rasmussen et al., 2019). We further propose that gait and other tests of physical function, when used in midlife, may not merely track age-induced deterioration, but instead reflect a life-course health status. Notably, scores on these tests have been shown to predict health and quality of life as individuals age. We will investigate how early this predictive power originates. We aim to answer the

questions: When does aging really begin? Do measures of physical function and cognitive function in midlife "hang together," forming the basis of collective deterioration with chronological age?

## Data analysis methods:

### Primary analyses:

The Dunedin study has several brain health measures at age 3 (neurological abnormalities, Peabody picture vocab test, Reynell receptive language test, Bayley motor test, lack of control rating) that are summarized using confirmatory factor analysis into a "brain health composite". This will be used in several primary analyses, described below.

1. We will summarize the physical function measures at age 45 (gait speed, step-in-place, chair stands, one-leg balance, grip strength) using confirmatory factor analysis into a "physical function composite."
    a. We hypothesize that the physical function measures assess a latent factor (coordination, central nervous system function) and it will be appropriate to create this composite.
2. We will assess the association between the age 3 brain health composite and the age 45 physical function composite.
    a. We hypothesize that better brain health at age 3 will be associated with better scores on the age 45 physical function composite.
3. We will assess the association between each component of the age 3 brain health composite with each component of the age 45 physical function composite.
4. At age 45, there is a variable that documents self-reported physical limitations. We will explore its association with the age 45 physical function composite and the age 3 brain health composite.
    a. We hypothesize that self-reported physical limitations will be highly correlated with the objective measures of physical function at age 45.
    b. We hypothesize that self-reported physical limitations will have similar correlations with age 3 brain health as the other physical function measures.
5. We will residualize all analyses for sex and socioeconomic status to explore whether any associations observed are merely an artifact of social class.

**Secondary analyses**:

1. We will assess the association between age 3 brain health composite and age 45 $VO_2$ max (maximum mL oxygen per kg body weight per minute when under respiratory exertion), a test of aerobic capacity that does not tap into brain function, as a negative control.
    a. We hypothesize that this association will be weaker than that between age 3 brain health and age 45 physical function.
2. We will assess the association between age 3 brain health composite and age 45 full-scale IQ (measured using the WAIS-IV).
    a. We can use this as a reference point to interpret the strength of association, if any, between age 3 brain health and age 45 physical function measures.

### Sensitivity analyses:

- Age 45 one-leg balance (eyes closed) will be binned due to the variable's non-normal distribution.
- Age 45 grip strength will be transformed into a "relative grip strength" variable by dividing maximum grip strength by the study member's body weight, due to the variable's non-normal distribution.
- In addition to age 45 gait speed that is the average of 3 walks (normal pace, fast as safely possible [maximum], while reciting alternate letters of the alphabet [dual task]), we will conduct analyses using only the average of the normal pace and maximum walk.

**General analysis methods**: Participants will be included if they have an age 3 brain health composite score and at least one measure of physical function at age 45. Models will use linear regression to investigate the association between age 3 brain health composite and physical function measures. All models will be run in R including sex and social class as covariates.

**Variables needed at which ages:**

**Age 3 motor, IQ, neurophysiology, language, and physical variables**

- Child brain integrity factor z-score
    - Neurological abnormalities
    - Peabody picture vocab test
    - Reynell receptive language test
    - Bayley motor test

**Age 3 temperament/behavior variables**

- Lack of control measure

**Age 45 physical function variables**

- Gait speed
- Chair stands
- Step-in-place
- One-legged balance, eyes closed
- Grip strength
- Self-reported physical limitations

**Age 45 activity/fitness variables**

- Adjusted VO2 max

**Age 45 cognition variables**

- Full-scale IQ, standardized
    - Verbal comprehension index
    - Perceptual reasoning index
    - Working memory index
    - Processing speed index

Sex as a demographic covariate
Social class as a demographic covariate

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

If midlife physical function is associated with early-life brain health, this will support the early systems integrity perspective on aging. The concepts of development and aging are currently separated into distinct entities in scientific literature. This study could provide an alternative perspective, positing that development and aging exist along the same conceptual path.

For clinicians, an association between age 45 physical function and age 3 brain health can have powerful implications about the utility of frailty indices. The physical function tests used for this analysis are accessible (do not require many tools nor much space to conduct) and can be used in many clinical settings. It may be useful to reconceptualize test performance as not only an indicator of musculoskeletal integrity but also a reflection of integrated health. Furthermore, this study can provide evidence for the utility of physical function tests in the context of lifelong development. Even though they are currently administered as tests of frailty, it may be the case that physical function tests can indicate lifelong deficit.

If the self-reported measure of physical limitations is correlated with performance on the physical function tests (and the physical function composite), this can also have implications for clinical practice. In cases in which clinicians do not have enough time to administer a full physical function battery, it is valuable to have evidence that one's subjective reports of frailty/physical function are consistent with objective measures.

In addition, if age 3 brain health is associated with adult IQ, it will support the notion that neurophysiological testing in childhood can have predictive power for adult cognitive functioning measured through comprehensive adult neuropsychological assessments (e.g., the WAIS-IV, the gold standard for adult IQ measurement). Overall, findings from this project will support future research on early-life predictors of aging and health outcomes.

**References cited:**

Deary, I. J. (2012). Looking for 'system integrity' in cognitive epidemiology. *Gerontology*, *58*(6), 545–553. https://doi.org/10.1159/000341157

Kennedy, B. K., Berger, S. L., Brunet, A., Campisi, J., Cuervo, A. M., Epel, E. S., Franceschi, C., Lithgow, G. J., Morimoto, R. I., Pessin, J. E., Rando, T. A., Richardson, A., Schadt, E. E., Wyss-Coray, T., & Sierra, F. (2014). Geroscience: Linking aging to chronic disease. *Cell*, *159*(4), 709–713. https://doi.org/10.1016/j.cell.2014.10.039

Rasmussen, L. J. H., Caspi, A., Ambler, A., Broadbent, J. M., Cohen, H. J., d'Arbeloff, T., Elliott, M., Hancox, R. J., Harrington, H., Hogan, S., Houts, R., Ireland, D., Knodt, A. R., Meredith-Jones, K., Morey, M. C., Morrison, L., Poulton, R., Ramrakha, S., Richmond-Rakerd, L., … Moffitt, T. E. (2019). Association of neurocognitive and physical function with gait speed in midlife. *JAMA Network Open*, *2*(10), e1913123. https://doi.org/10.1001/jamanetworkopen.2019.13123

## Data Security Agreement

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

**Signature: J Kathy Xie**