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HUMAN DEVELOPMENT, BIRTH TO DEATH

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Concept Paper Form

Provisional Paper Title: Exercising your way to a youthful brain: Is cardiovascular fitness associated with brainAGE?
Proposing Author: Tracy d'Arbeloff
Author's Email: Tracy.Darbeloff@duke.edu
P.I. Sponsor: Ahmad Hariri, Terrie Moffitt, Av Caspi (if the proposing author is a student or colleague of an original PI)
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Please describe your proposal in 2-3 pages with sufficient detail for helpful review.

Objective of the study:

Large-scale efforts are underway to identify effective interventions to buffer against age-related cognitive decline, which represents a significant public health concern (Burns et al., 2008; Deary et al., 2009; Dougherty et al., 2017). One possible intervention of recent focus is improving cardiovascular fitness (Belsky et al., 2015; Chapman et al., 2013; Deary et al., 2009; Hayes et al., 2013a). Increased cardiovascular fitness has been associated with a plethora of physical benefits including increased bone mass, increased mobility, and decreased risk of heart disease (Belsky et al., 2015; Erickson et al., 2014; Firth et al., 2018). Cardiovascular fitness has also been linked to changes in brain structure and cognitive function—making it a possible mechanism to intervene against age-related decline (Belsky et al., 2015; Deary et al., 2009; Firth et al., 2018; Jonasson et al., 2017). Specifically, better cardiovascular fitness has been associated with three features of structural brain integrity: higher cortical thickness and surface area, greater hippocampal grey matter volume, and higher white matter microstructural integrity (Erickson et al., 2014; Hayes et al., 2013a, 2013b; Jonasson et al., 2017; d'Arbeloff et al., 2020).

However, it is unknown if cardiovascular fitness is directly associated with brain aging in these structural measures that underly cognitive decline. Additionally, it is unclear if such associations are measurable in midlife when interventions can stave off age-related atrophy before it has accrued in the brain. While associations between cardiovascular fitness and various measures of

brain structure offer some precursory evidence, looking at associations with these structures independently is not the most intuitive way to estimate future risk for clinically significant aging-related decline. This is because it is difficult to quantify comparative deviations from normal aging-related brain atrophy using only isolated cross-sectional measures of brain structure as various structural measures in the brain follow different aging trajectories. For example, as measures of surface area and cortical thickness are not highly correlated and are shaped by different biological mechanisms throughout the aging process, their cross-sectional associations with age-relevant biomarkers may differ (Cox et al., 2020; Fjell et al., 2015; Lemaitre et al., 2012). Such divergent associations make it difficult to discern cohesive patterns of atrophy across the brain associated with cognitive decline.

One recently developed measure that may offer a way to bridge this issue is called "brain age." As with biological age—an estimate of age that weights chronological age by individual differences in accelerated age-related biological degeneration in the body(Ludwig & Smoke, 1980)—brain age quantifies individual rates of aging-related atrophy for different measures (e.g., cortical thickness, surface area, grey matter volume) into a single comprehensive measure of the overall condition of the brain (Cole & Franke, 2017; Elliott et al., 2019). Brain age is calculated using machine learning algorithms that predict chronological age from structural MRI measures (Liem et al., 2017). The difference between an individual's age predicted by their MRI data and an individual's chronological age is called the brain Age Gap Estimate (brainAGE).

Finding associations between cardiovascular fitness and brainAGE would build on initial associations between fitness and individual measures of brain structure. Further, it would help provide evidence that fitness may be specifically relevant for brain aging. However, this association has yet to be explicitly tested. The objective of this study is to utilize longitudinal data from the Dunedin Study to investigate associations between brainAGE at age 45 and not only contemporaneous cardiovascular fitness, but also rate of decline in cardiovascular fitness from age 26 to 45, to establish further evidence that cardiovascular fitness may be a viable intervention against brain aging indicative of higher risk for later development of cognitive impairment and dementia.

Data analysis methods:

- Linear regression (using R) will be used to assess straightforward associations between fitness (VO2max) and brainAGE, as well as between the rate of change in fitness over time and brainAGE

- Structural Equation Modeling will be used to calculate the rate at which each individual's fitness has declined over the past two decades. Extracted slopes will be used as a measure of the rate of decline in fitness in analyses.

Variables needed at which ages:

VO2max (Ages: 26, 32, 38, 45)
childhood IQ (7, 11, 13→ AVG)
Fsiq45a (Age 45)
BrainAGE (Age 45)
Sex

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

Fitness interventions, if valid, are an easy, affordable, and accessible option to utilize against age-related cognitive decline. RCTs are already underway—with positive results. However, associations between fitness and brain structure are rarely age-specific. As such, it is unclear if fitness has any benefit to individuals who show accelerated aging trajectories above and beyond normal aging. Finding associations between cardiovascular fitness and brainAGE would build on initial associations between fitness and individual measures of brain structure. Further, it would help provide evidence that fitness may be specifically relevant for brain aging.

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