Concept Paper Template

Provisional Paper Title: Cardiovascular Fitness and the Midlife Brain

Proposing Author: Tracy d'Arbeloff

Author's Email: Tracy.Darbeloff@duke.edu

P.I. Sponsor: Ahmad Hariri, Avshalom Caspi, Terrie Moffit

Today's Date: 02/21/2019

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

Objective of the study:

Neurological and cognitive decline associated with aging represents a significant public health concern in rapidly aging Western societies (Burns et al., 2008; Deary et al., 2009; Dougherty et al., 2017). Large-scale efforts are underway to identify effective interventions to buffer against or even reverse age-related cognitive and neurological decline. One possible intervention of recent focus is improving cardiovascular health and fitness (Burns et al., 2008; Deary et al., 2009; Dougherty et al., 2017).

Increased cardiovascular fitness is associated with a plethora of physical benefits including increased bone mass, increased mobility, and decreased risk of heart disease (Belsky et al., 2015; Erickson, Leckie, & Weinstein, 2014; Firth et al., 2018). Cardiovascular health and fitness have also been linked to changes in brain structure and cognitive function—making it a possibly intervenable surrogate biomarker of age-related decline (Belsky et al., 2015; Deary et al., 2009; Firth et al., 2018; Jonasson et al., 2017). Specifically, cardiovascular fitness has been associated with increased cortical thickness and surface area, greater hippocampal grey matter volume, and higher white matter microstructural integrity, (Jonasson et al., 2017).

However, recent studies by Belsky et al. and Deary et al. have indicated that much of the positive benefits and associations seen between fitness, cognition, and the brain can be explained by higher IQ in childhood. This suggests that rather than higher fitness acting as a protective buffer, it may instead be just another facet of neuroselection (Belsky et al., 2015; Deary et al., 2009). For example, one possibility is that children with higher IQ tend to make healthier life choices and have access to better resources, which in turn leads to better cardiovascular fitness and brain health (Belsky et al., 2015; Deary et al., 2009). As such, studies targeting fitness as a potential biomarker for intervention need to take into account any neuroselective influences, such as childhood IQ or related polygenic scores. Yet few studies—if any—control for neuroselective variables as potential confounding factors when evaluating effects of cardiovascular fitness (Belsky et al., 2015; Deary et al., 2009; Jonasson et al., 2017).

The objective of this study is to utilize our access to longitudinal data from the Dunedin Study to disentangle effects of cardiovascular fitness on brain structure from those associated with childhood IQ.

Data analysis methods:

- Linear regression (using R) will be used to assess straightforward associations between fitness (VO2max) and various structural brain phenotypes.
- Structural Equation Modeling and trajectory modelling will be used to look at how different fitness trajectories and changes in fitness across the lifespan load onto brain structure.

Variables needed at which ages:

VO2max (15,26,32,38,45)
Wfsiq713
Fsiq45a
sportsMetsWk38
sportHrsWk38
sprthr32grp012
SprtHr38grp012
PersistAct3238
Polygenetic scores (GWAS) for brain structure (i.e., Cortical Thickness)
Total and regional Cortical Thickness
Total and regional Surface Area
Total and subcortical Grey Matter Volume
Total Intracranial Volume
Voxel-wise fractional anisotropy
Sex
Smoking

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 neurological and cognitive decline in the general population. RCTs are already underway—with positive results. However, in order to establish the validity of fitness as an intervention target, the field must A. discern what, if any, are the neuroprotective benefits of fitness in the brain, and B. if these effects survive controlling for childhood IQ. This will allow us to gain a broader understanding of exactly how and where in the brain targeted cardiovascular fitness interventions may help to slow or prevent general age-related neurological changes in the normal population as well as in those most at risk for age-related neurological and cognitive decline.

References cited:

Belsky, D. W., Caspi, A., Israel, S., Blumenthal, J. A., Poulton, R., & Moffitt, T. E. (2015). Cardiorespiratory fitness and cognitive function in midlife: Neuroprotection or neuroselection?: Fitness and Cognitive Function. *Annals of Neurology*, *77*(4), 607–617. https://doi.org/10.1002/ana.24356

Burns, J. M., Cronk, B. B., Anderson, H. S., Donnelly, J. E., Thomas, G. P., Harsha, A., … Swerdlow, R. H. (2008). Cardiorespiratory fitness and brain atrophy in early Alzheimer disease, 8.

Chapman, S. B., Aslan, S., Spence, J. S., DeFina, L. F., Keebler, M. W., Didehbani, N., & Lu, H. (2013). Shorter term aerobic exercise improves brain, cognition, and cardiovascular fitness in aging. *Frontiers in Aging Neuroscience*, *5*. https://doi.org/10.3389/fnagi.2013.00075

Deary, I. J., Corley, J., Gow, A. J., Harris, S. E., Houlihan, L. M., Marioni, R. E., … Starr, J. M. (2009). Age-associated cognitive decline. *British Medical Bulletin*, *92*(1), 135–152. https://doi.org/10.1093/bmb/ldp033

Dougherty, R. J., Schultz, S. A., Boots, E. A., Ellingson, L. D., Meyer, J. D., Van Riper, S., … Cook, D. B. (2017). Relationships between cardiorespiratory fitness, hippocampal volume, and episodic memory in a population at risk for Alzheimer's disease. *Brain and Behavior*, *7*(3), e00625. https://doi.org/10.1002/brb3.625

Erickson, K. I., Leckie, R. L., & Weinstein, A. M. (2014). Physical activity, fitness, and gray matter volume. *Neurobiology of Aging*, *35*, S20–S28. https://doi.org/10.1016/j.neurobiolaging.2014.03.034

Firth, J., Stubbs, B., Vancampfort, D., Schuch, F., Lagopoulos, J., Rosenbaum, S., & Ward, P. B. (2018). Effect of aerobic exercise on hippocampal volume in humans: A systematic review and meta-analysis. *NeuroImage*, *166*, 230–238. https://doi.org/10.1016/j.neuroimage.2017.11.007

Jonasson, L. S., Nyberg, L., Kramer, A. F., Lundquist, A., Riklund, K., & Boraxbekk, C.-J. (2017). Aerobic Exercise Intervention, Cognitive Performance, and Brain Structure: Results from the Physical Influences on Brain in Aging (PHIBRA) Study. *Frontiers in Aging Neuroscience*, *8*. https://doi.org/10.3389/fnagi.2016.00336

Data Security Agreement

Provisional Paper Title	Cardiovascular Fitness and the Midlife Brain
Proposing Author	Tracy d'Arbeloff
Today's Date	02/28/19

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

Please initial your agreement

X	I am current on Human Subjects Training (CITI (www.citiprogram.org) or equivalent)
X	My project is covered by Duke or Otago ethics committee OR I have /will obtain ethical approval from my home institution.
X	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.
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 Professor Moffitt or Caspi. (919-684-6758, tem11@duke.edu, ac115@duke.edu)
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 Terrie or Avshalom 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: ______Tracy C. d'Arbeloff______________________________