

**Concept Paper Form**

<b>Provisional Paper Title:</b> <i>Is microstructural integrity of whole-brain white matter tracts associated with midlife fitness?</i>
<b>Proposing Author:</b> Tracy d'Arbeloff
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<b>P.I. Sponsor:</b> Ahmad Hariri, Terrie Moffitt, Av Caspi (if the proposing author is a student or colleague of an original PI)
<b>Today's Date:</b> 7/1/2020

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

**Objective of the study:**

White matter is a facet of brain structure that often receives less focus in basic neuroscience and brain-aging research than grey matter variables like cortical thickness and hippocampal volume (Liu et al., 2017). However, white matter atrophy and associated disorders (i.e., white matter hyperintensities, lunar infarcts, etc) are common, age-related aspects of brain structure used by neurologists in clinical settings (Dickie et al., 2016; Habes et al., 2016; Marin & Carmichael, 2019; Wardlaw et al., 2015). In fact, research suggests that changes in white matter may be more related to behavioral symptoms of brain aging (e.g., cognitive decline) than changes in grey matter and that white matter may be more susceptible to aging-related neurological disorders like aging-related dementias (ARD) (Araque Caballero et al., 2018; Liu et al., 2017; Mito et al., 2018; Wen et al., 2019). Microstructural integrity of white matter tracts in the brain, measured using diffusion tensor imaging (DTI), have been used as proxies of overall white matter degradation (Lee et al., 2015; Liu et al., 2017; Wen et al., 2019). Further, research suggests that aging-specific white matter changes associated with risk for ARD, such as white matter hyperintensities, may be fiber-specific (Mito et al., 2018). In other words, DTI tractography may offer a way to localize white matter degradation to certain tracts specifically associated with cognition or other relevant behavioral traits (Mito et al., 2018; Wen et al., 2019).

As changes in white matter, like those seen in grey matter, are apparent years before any clinical symptoms present (Araque Caballero et al., 2018), preventing or delaying aging-related white matter degradation may provide novel therapeutic strategies that could aid in delaying brain aging. For example, vascular risk factors (e.g., high blood pressure, obesity, smoking) and cardiovascular or cerebrovascular disease are thought to be major contributors to aging-related white matter atrophy. Thus, one strategy that may target changes in white matter, potentially through impacting vascular health, is cardiovascular fitness (Vesperman et al., 2018). Studies on rats have shown that increasing motor activity modulates both myelin and underlying white matter tracts and human adults who engage in higher levels of physical activity show better white matter structural integrity (Liu et al., 2017; Perea et al., 2016; Sexton et al., 2016). However, recent clinical trials targeting changes in white matter through increasing physical activity to mitigate aging-related decline have found mixed results.

The lack of positive results could be due to several factors. For example, many of these interventions target populations of older adults already showing clinical symptoms of ARD (Sexton et al., 2016). As white matter degradation is apparent years before clinical symptoms appear, it could be that interventions are being staged too late in life after too much damage has accrued. It could also be that increasing physical activity may not be sufficient to enact change in cardiovascular fitness, and thus may not result in any white matter changes. Other health behaviors, such as smoking, obesity, and alcohol consumption, may be more effective in targeting changes in cardiovascular health (Lourida et al., 2019). The purpose of this study is to look at associations between cardiovascular fitness, health and fitness behaviors, and white matter tractography in midlife—a time when white matter may have started to degrade but clinical symptoms have yet to present. Both the UK Biobank and the Dunedin Cohort will be utilized.

Recent research has implicated lower structural integrity in white matter tracts underlying the default mode network as indicative of greater risk for cognitive decline ARD (Brown et al., 2018; Mito et al., 2018; Noonan et al., 2018). Thus, tracts associated with the default mode, including midline association tracts (e.g., cingulum), long cortico-cortical lateral association tracts (e.g., sagittal striatal and superior longitudinal fasciculus) and cross-hemispheric pathways (e.g., forceps major and forceps minor), may be more vulnerable to aging-related phenotypes and may be most predictive of fitness and health behaviors. However, as this analysis is data-driven and somewhat exploratory in

nature, I will not limit or exclude white matter tracts from analyses based on *a priori* hypotheses. I do hypothesize that smoking and diet will show stronger associations with both cardiovascular fitness and white matter integrity as both are well-validated vascular risk factors associated with cardiovascular disease and risk for ARD.

**Data analysis methods:**

→ Cross-validated predictive modeling (specifically elastic net modelling) will be used to predict cardiovascular fitness from whole brain white matter tract integrity. Elastic net is a regularized regression method that incorporates penalties,  $\lambda_1$  and  $\lambda_2$ , from both LASSO and RIDGE regression to minimize both bias and variance in base ordinary least square (OLS) models (on, n.d.):

To do the analyses, VO2Max scores and white matter tract fractional anisotropy scores from the Dunedin data will be split into a training dataset (70%) and a test dataset (30%). Using the training data, 10-fold cross-validation will be used to determine the best  $\alpha$  and  $\lambda$  values that correspond to the lowest prediction error. These parameters will then be used in fitting the data to the model and obtaining predicted VO2Max values from whole-brain white matter tractography. Finally, actual VO2Max scores will be correlated with model-predicted scores to get a measure of the predictive capacity of the overall model. This will give a measure of in-sample prediction. The same analysis will then be run within the UK Biobank dataset.

I then plan to compare the predictive models between datasets. Using a subset of white matter tracts that both datasets share, I will train each model within dataset, and then predict values between datasets (i.e., training model using the Dunedin dataset, then use the UK Biobank as a novel test dataset to generate predicted values). This will allow me to compare across samples as well as within samples. In addition, it will allow me to contrast the relative comparability of PWC<sub>75%</sub> in UK Biobank and the VO<sub>2</sub>Max in Dunedin as measures of cardiovascular fitness.

The use of elastic net modeling will not only allow me an unbiased, cross-validated way to test if white matter tract integrity throughout the brain is associated with cardiovascular fitness, but also which tracts contribute the most weighted predictive power across the brain. By using the Lourida et al. health index, I also hope to repeat the above analyses to test various health behaviors to assess relative correlation strength with both cardiovascular fitness and white matter integrity. This could

help inform future lifestyle interventions as to which health behaviors may be best at affecting change in vascular and cerebrovascular risk. Post-hoc analyses on any significantly predictive white matter tracts will be run to test laterality.

**Variables needed at which ages:**

Dunedin:

- VO2max (Age 45)
- If feasible: PWC<sub>75%</sub>
- Lourida et al. Health Index (Age 45)
- Sex
- Mean FA values for White Matter Tracts (L & R hemispheres) (Age 45)
  - TRACTS:
    - Anterior Thalamic Radiata
    - Cingulum tract
    - Cingulum hippocampal tract
    - Corticospinal tract
    - Forceps Major
    - Forceps Minor
    - Sagittal Striatal
    - Middle cerebellar peduncle
    - Superior thalamic radiata
    - Medial lemniscus
    - Superior Longitudinal
    - Uncinate fasciculus

UK Biobank

PWC<sub>75%</sub>

Age at assessment

Age at scan visit

Month of birth

Year of birth

Sex

Assessment center

Assessment center (scanner visit)

Lourida et al. Health Index

Mean FA values for White Matter Tracts (L&R Hemispheres)

TRACTS:

- Anterior Thalamic Radiata
- Cingulum tract
- Cingulum hippocampal tract
- Corticospinal tract
- Forceps Major
- Forceps Minor
- Sagittal Striatal
- Middle cerebellar peduncle
- Superior thalamic radiata

- Medial lemniscus
- Superior Longitudinal
- Uncinate fasciculus

**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. White matter tracts are particularly vulnerable to aging-related degeneration and are hypothesized to be intricately involved in risk for cognitive decline. If white matter tracts across the brain do predict cardiovascular fitness levels, this would offer data-driven evidence to support findings that fitness may be a way to mitigate age-related white matter tract atrophy. Further, it may help raise awareness of the importance of white matter microstructural integrity in studies of aging in the brain, especially in those already at risk for cardiovascular disease.

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## Data Security Agreement

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<b>Today's Date:</b> 7/1/2020

<input checked="" type="checkbox"/>	I am current on Human Subjects Training (CITI ( <a href="http://www.citiprogram.org">www.citiprogram.org</a> ) or equivalent)
<input checked="" type="checkbox"/>	My project is covered by the Duke ethics committee OR I have /will obtain ethical approval from my home institution.
<input checked="" type="checkbox"/>	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.
<input checked="" type="checkbox"/>	I will not "sync" the data to a mobile device.
<input checked="" type="checkbox"/>	In the event that my laptop with data on it is lost, stolen or hacked, I will immediately contact Moffitt or Caspi.
<input checked="" type="checkbox"/>	I will not share the data with anyone, including my students or other collaborators not specifically listed on this concept paper.
<input checked="" type="checkbox"/>	I will not post data online or submit the data file to a journal for them to post.  <i>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>
<input checked="" type="checkbox"/>	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.  This 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