RVC Concept Paper

Provisional Paper Title: Retinal Vessel Caliber Predicts Prevalence of White Matter Abnormalities in Middle Aged Adults

Proposing Author: Tracy d'Arbeloff (Working with Max Elliott and Annchen Knodt)

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

Today's Date: May 8th, 2018

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

Objective of the study:

Our objectives are to:

1) Replicate findings of associations between changes in retinal vessel caliber and white matter lesions in older/aging adults, using novel analytical methods geared towards lesions caused by cerebral microvasculature damage. Our main hypothesis is that wider venular caliber (at age 38 and at age 45) will predict prevalence of white matter lesions. We will also investigate whether narrower arteriole caliber is predictive of white matter lesions as well.

2) Investigate correlations between retinal vessel caliber and overall white matter structural integrity in middle aged adults. Our hypothesis is that wider retinal vessel caliber is associated with reduced FA values, specifically in cingulum bundle, and potentially reduced global white matter integrity as a whole.

Research suggests disease of smaller arterioles and arteries may be a major risk factor for age related neurological issues, such as stroke, Alzheimer's, dementia, and cognitive decline, as well as a strong indicator of MRI-defined white matter lesions (Cooper et al., 2006; Liew et al., 2014; Sun, Wang, Mackey, & Wong, 2009; Yatsuya et al., 2010). White matter lesions are, in turn, hypothesized to be a biomarker for microvascular disease, stroke, and increased cerebrovascular risk factors (Cooper et al., 2006; Knopman, 2007; Liew et al., 2014; Sun et al., 2009; Yatsuya et al., 2010). Multiple studies have linked wider retinal venular caliber with MRI-defined white matter lesions, as well as with measures of cerebral microvasculature (Heringa et al., 2013; Sun et al., 2009). One hypothesis for this association is that wider venules may denote problems with oxygen supply to the brain as they are thought to reflect structural damage to the microvasculature

(Meier et al., 2013; Sun et al., 2009). Replicating the association between retinal vessel caliber changes and white matter lesions in middle-aged adults would provide further evidence that retinal vessel imaging can provide proxy measures of aspects of cerebral health, at earlier ages than previously shown.
Beyond white matter lesions, changes in retinal vessel caliber have been linked with poor white matter microstructure, as measured by FA values, which suggests that retinal vessel caliber measures may be related to more widespread deficits in white matter beyond visible lesions (Mutlu et al., 2016). In addition, abnormal retinal vasculature has been linked with general cognitive deficits (Heringa et al., 2013; Shalev et al., 2013; Wong et al., 2002) as well as disorders with prevalent cognitive symptoms, such as Schizophrenia and Alzheimer's (Meier et al., 2013; the AIBL Research Group et al., 2013). Symptoms associated with altered cognitive abilities are associated with lower white matter structural integrity of multiple white matter tracts, including the cingulum bundle in particular (Lee et al., 2015; Shepherd, Laurens, Matheson, Carr, & Green, 2012; Tuladhar et al., 2015). Thus, a logical next step is to see if retinal vessel caliber (specifically wider venular caliber) is independently related to white matter lesions, further linking it with structural biomarkers of cognitive faculties.

Data analysis methods:

To generate measures of white matter lesion prevalence, we will use either BIANCA protocol (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/BIANCA) or UBO (https://cheba.unsw.edu.au/group/neuroimaging-pipeline), which were trained using vascular cohorts and demonstrate reliable identification of white matter lesions (Griffanti et al., 2016; Jiang et al., 2018). The BIANCA protocol requires training on a subset (10-20) of the Dunedin cohort with manually defined white matter lesions (by an experienced neurologist). While the UBO is fully automated and does not require manual training, it is unclear which is ideal for our specific scanner protocol and population, therefore we will test both and optimize for our sample.

Diffusion tensor images are processed according to the protocol developed by the Enhancing Neuro Imaging Genetics Through Meta-Analysis consortium (Jahanshad et al., 2013). In brief, raw diffusion-weighted images undergo eddy current correction and linear registration to the non-diffusion weighted image in order to correct for head motion. These images are skull-stripped and diffusion tensor models are fit at each voxel using the FMRIB's Diffusion Toolbox (FDT; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT). This produces a whole-brain fractional anisotropy (FA) image for each participant, which is next processed using tract-based spatial statistics (TBSS) in FMRIB's Software Library (FSL; Smith et al., 2006). FA images are then realigned to the FMRIB standard-space FA image and transformed into MNI standard space. A mean FA skeleton is created and thresholded at .2, and each participant's FA data are projected onto the skeleton. Regions of interest are then created using the Johns Hopkins University White Matter Tractography Atlas (Mori et al, 2005)

Once we have extracted measures relating to white matter integrity and lesions, the statistical software R (v. 3.4.4) will be used to run linear regression to test for predictive relationships. All code will be made available.

Variables needed at which ages:

Retinal Vessel Caliber (Age 38 and Age 45)
T1 and FLAIR MRI images (45)
Extracted FA values (45)
WFSIQ
sTORTa (simple tortuosity Arteriole)
cTORTa (curvature tortuosity arteriole)
sTORTv (simple tortuosity venule)
cTORTv (curvature tortuosity arteriole)

Controlling for confounds:

Exclude those with MS diagnoses and brain damage (alternative reasons for major white matter abnormalities)

Graham: What other potential confounds should be considered (or are usually controlled for) when looking at retinal data?

- Potentially: Sex, smoking, blood pressure?

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

Retinal vessel imaging has emerged as a promising new method for investigating complex neurological issues. However, the degree to which altered retinal microvascular is a good indicator of cerebral structure and function is still unclear. Finding correlations between retinal vessel imaging and brain structure (such as abnormalities in integrity and structure of white matter) will further inform the extent that retinal imaging, and retinal vessel caliber specifically, can capture pathology of the brain, thereby offering a unique tool to aid basic brain research. Retinal imaging has potential to be a more accessible and cost-effective method to measure brain abnormalities than current measures like MRI, which require much more time, money, and equipment (Xu et al., 2016). If changes in retinal vasculature are concretely linked with clinically significant white matter abnormalities, then retinal vessel imaging could further emerge as a fast, simple way to investigate new avenues of neuroscientific inquiry in vivo, as well as a powerful clinical diagnostic tool. In particular, if retinal imaging is linked to brain abnormalities in mid-age, it would provide evidence for clinical utility of retinal imaging as an early screening tool for aging related brain pathology. Beyond retinal vessel imaging, this study will further validate white matter lesion pipelines for broader use clinical and basic research.

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Data Security Agreement

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Proposing Author	Tracy d'Arbeloff
Today's Date	May 14, 2018

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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.*
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Signature: ___*Tracy d'Arbeloff*_____

CONCEPT PAPER RESPONSE FORM

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Provisional Paper Title	Retinal Vessel Caliber Predicts Prevalence of White Matter Abnormalities in Middle Aged Adults
Proposing Author	Tracy d'Arbeloff & Max Elliott (potential dual first authorship)
Other Contributors	Annchen Knodt, Ahmad Hariri, Terrie Moffitt, Avshalom Caspi, Ross Keenen, Tracy Meltzer, Richie Poulton, Sandhya Ramrakha, David Ireland, Graham Wilson
Potential Journals	
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	Conceptualizing and collecting one or more variables
	Data collection
	Conceptualizing and designing this specific paper project
	Statistical analyses
	Writing
	Reviewing manuscript drafts
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