DUNEDIN STUDY CONCEPT PAPER FORM

Provisional Paper Title: Associations between retinal nerve fibre layer and ganglion cell layer and cognition from childhood to middle age

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P.I. Sponsor: Richie Poulton
(if the proposing author is a student or colleague of an original PI)

Today's Date: 23 June 2021

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

Objective of the study:

To examine whether retinal measures attained via optical coherence tomography (OCT), i.e. retinal nerve fibre layer (RNFL) and ganglion cell layer (GCL) thicknesses, are associated with cross-sectionally with cognitive function at age 45 and longitudinally from childhood. Further, to investigate whether RNFL and GCL are associated with cognitive decline over this period.

Data analysis methods:

Multiple regression.

Variables needed at which ages:

Cognitive variables:

- Full scale IQ, performance IQ, verbal IQ, and subscale scores, ages 7, 9, 11
- Full scale IQ, WAIS indices, and subscale scores, age 45
- Residualised IQ change

Vision variables:

- RNFL (average and quadrants)
- GCL (average and segments)
- Intraocular pressure
- Axial length
- Optic disc area

Covariates:

- Sex

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

Alzheimer's disease and other dementias are currently incurable, and given the complexity of these diseases and their proliferation in our aging population, it is important to develop technologies to identify pre-clinical signs of disorder and monitor disease progression (MacGillivray et al., 2014). Early identification of dementia may be important for setting up management plans to help slow or manage the progression of the illness. In the future, as treatments are developed, early identification may be useful for prevention or treatment of dementia.

Diagnoses of dementia are rare in middle age, but the early processes of cognitive decline may be evident by the fourth decade of life (Shalev et al., 2013). This study seeks to investigate whether there is an association between thickness of the RNFL and GCL, measured by OCT, and cognitive functioning, both concurrently (at age 45) and across the lifespan, from age 7.

Understanding what is happening in the brain in the early stages of cognitive decline may be critical for understanding the process of neurodegeneration in mild cognitive impairment and other dementias. As the retina can be easily and non-invasively imaged, this provides us with a unique opportunity to visualise the living brain and observe changes in neuroanatomy over time.

The retina shares similar embryological development to the brain, and thus shares many neurophysiological features with the cortex (Nguyen et al., 2017). While most research with OCT has focused on ophthalmological diseases, some research has used OCT to investigate changes in the retina that occur in patients with dementia (Cameron & Tatham, 2016; Moreno-Ramos, Benito-León, Veillarejo-Galende, & Bermejo-Pareja, 2013), although evidence is strongest for Alzheimer's disease and mild cognitive impairment (Thomson, Yeo, Waddell, Cameron, & Pal, 2015). The retina appears to reflect the pathological processes typical of dementia (Chan et al., 2017), and retinal biomarkers have been associated with Alzheimer's disease (AD) and mild cognitive impairment (MCI; den Haan, Verbraak, Visser, & Bouwman, 2017). In the same cohort as the present study, retinal vessel calibre was associated with cognitive functioning across the lifespan, from childhood (age 7) to adulthood (age 38; Shalev et al., 2013). However, research into retinal neuroanatomy as an indicator of cognitive performance over the life span is limited. A recent study found that thinner RNFL was associated with poorer cognitive functioning in adults aged 40-69, and that thinner RNFL at baseline was associated with greater decline in cognitive functioning 3 years later (Ko et al., 2018). RNFL thinning was also found to be greater in people who converted to MCI or AD (Shi et al., 2014). Our study can expand on these findings by comparing cognitive performance from childhood and midlife in a population-based cohort.

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DATA SECURITY AGREEMENT

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

Please initial your agreement: (customize as necessary)

Y	I am current on Human Subjects Training [CITI www.citigrogram.org] or equivalent.
Y	My project is covered by the Dunedin Study's ethics approval OR I have /will obtain ethical approval from my home institution (please specify).
Y	I will treat all data as "restricted" and store in a secure fashion. My computer or laptop is: • encrypted (recommended programs are FileVault2 for Macs, and Bitlocker for Windows machines) • password-protected • configured to lock-out after 15 minutes of inactivity AND • has an antivirus client installed as well as being patched regularly.
Y	I will not "sync" the data to a mobile device.
Y	In the event that my laptop with data on it is lost, stolen or hacked, I will immediately contact my PI Sponsor or Study Director, Richie Poulton (richie.poulton@otago.ac.nz).
Y	I will not share the data with anyone, including my students or other collaborators not specifically listed on this concept paper.
Y	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 your PI Sponsor or Richie Poulton for strategies for achieving compliance with data-sharing policies of journals.*
Y	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: _Ashleigh Barrett-Young_____