DUNEDIN STUDY CONCEPT PAPER FORM

Provisional Paper Title: Hearing across the lifecourse and associated changes in the brain

Proposing Author: Kirsten Cheyne

Author's Email: Kirsten.cheyne@otago.ac.nz

P.I. Sponsor: Suzanne Purdy and Peter Thorne
(if the proposing author is a student or colleague of an original PI)

Today's Date: 10 October 2022

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

Objective of the study:

Several large-scale studies show an association between hearing acuity loss and increased rates of cognitive decline (Humes et al., 2013), with peripheral hearing loss accounting for up to 24% increased risk for incident cognitive impairment (Lin et al., 2013) and a reported 8.2% contribution of risk for dementia at a population level (Livingston et al., 2020).

A number of hypotheses to explain the association between hearing loss and dementia have been proposed. For example, the Common Cause Theory in Aging (Lindenberger & Baltes, 1994) suggests that sensory and cognitive systems decline in parallel and share a common underlying pathology of the ageing process. The Cognitive Load Hypothesis (Lemke & Besser, 2016) suggests that stronger reliance on neural networks involved in cognitive processing (and therefore reduced cognitive capacity) could contribute to the acceleration of cognitive decline in older adults with hearing loss.

Ageing and hearing loss have been shown to underlie measurable atrophy of cortical auditory regions (Peelle & Wingfield, 2016). Atrophy of cortical auditory regions has

been measured in varying ways in both the white and gray matter of the brain (Manno et al., 2021), including cortical thinning (Ha et al., 2020), integrity of microstructures measured via diffusion tensor imaging (Croll et al., 2020; Fan et al., 2019; Rigters et al., 2018), and auditory pathway tractography (Profant et al., 2014).

The majority of these studies are limited as they typically involve cross-sectional cohorts of older adults. Our proposed project takes advantage of the attributes of the Dunedin Study, which allow for a unique approach to this field, given that all study members are of the same age, and that their health and development have been measured in-person from birth. The Dunedin Study also has high-quality MRI scans from the brains of study members at mid-life (age 45). Although 45 is typically too young to see substantial clinical hearing loss or significant cognitive decline, we have evidence already of significant hearing acuity shifts in this population from childhood to midlife, and can use this rich and unique resource to investigate links between hearing and brain structure.

The aim of this study is to investigate how changes in hearing acuity and auditory processing affect brain structure and integrity as a person ages. We hypothesise that we will observe specific neurological trends associated with hearing in midlife, and that these will be independent of "pace of ageing" (biological) and "brainAGE" (neural) factors that have been derived from Dunedin Study data.

Data analysis methods:

We will work with the MRI group at Duke University to produce summary measures of cortical thickness and regional tract-based and voxel-wise white matter microstructural integrity and white matter hyperintensity volume.

To test for associations between both hearing acuity (peripheral hearing) and central auditory processing at age 45 and measures of brain structure, we will follow a two-part analysis strategy. For all analyses, the outcome variables will include global measures of total brain volume (TBV), mean cortical thickness (CT), total surface area (SA), average fractional anisotropy (FA), and brainAGE (a prediction of brain health generated from MRI scans at age 45), as well as regional measures of CT, SA, FA, and subcortical volumes. We will control for otological status in childhood (a composite score that includes pure tone audiometry and tympanometry measures from ages 5, 7, and 9, and history of ear disease in childhood). Hearing acuity is measured by pure tone audiometry (hearing tones presented at different pitches and volumes). Central auditory processing is measured using LISN-S; a test of spatial auditory processing.

We will repeat these analyses adjusting for general systems decline ("pace of ageing"), neurodegeneration due to biological age ("brainAGE"), and other relevant covariates such as SES, sex, and adult IQ.

Variables needed at which ages:

Primary independent variables

- Childhood otological status
- Adult (P45) pure-tone audiometry (peripheral hearing)
- P45 LiSN-S (central auditory processing)

Primary dependent variables

Global measures of brain structure:

- Mean Cortical Thickness (CT)
- Total Surface Area (SA)
- Average Fractional Anisotropy (FA)
- White matter hyperintensity volume
- Brain-Age Gap Estimate (brainAGE) – difference between estimated brain age and chronological age

Regional measures of brain structure:

- Regional measures of cortical thickness from the 360 regions in the multi-modal cortical parcellation described in Glasser et al. 2016
- Regional measures of surface area from the same 360 regions
- Tract-wise measures of fractional anisotropy from the Johns Hopkins University white matter atlas (24 bilateral tracts; Wakana et al., 2007).
- Regional GMV of 20 subcortical structures from Freesurfer (Fischl et al., 2002)
- Inferior Colliculus Grey Matter Volume (GMV)
- Medial Geniculate Nucleus of the Thalamus (MGN) Grey Matter Volume (GMV)

Covariates

- Pace of aging at age 45
- BrainAge (at age 45)
- Adult IQ – processing speed
- Childhood brain-health
- Sex
- SES
- Total Brain Volume (TBV)
- Intracranial Volume (ICV)

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

Decline in mental capabilities such as working memory, executive functions, processing speed, and reasoning are common in the healthy ageing process (Deary et al., 2009; Peelle & Wingfield, 2016; Spreng, Wojtowicz & Grady, 2010). There is a high degree of variability in the extent of cognitive deficits among older adults (Brayne, 2007; Spreng, Wojtowicz & Grady, 2010), with some individuals with cognitive impairment remaining "healthy", while others progress to more severe conditions such

as mild cognitive impairment (MCI) or dementia (Bidelman et al., 2017).

MCI is characterised by difficulties in memory, language, thinking and judgement beyond what is expected, but not to the extent of severely impacting daily life, and is a precursor to dementia (Livingston et al., 2020; Petersen, 2011; Roberts & Knopman, 2013), although not all cases of MCI progress to dementia (Bidelman et al., 2017). Hearing impairment is one of 12 modifiable risk factors identified by the 2020 Lancet Commission on dementia prevention, intervention, and care (Livingston et al., 2020). A recent New Zealand-specific study (Ma'u et al., 2021) found that, compared to global estimates, New Zealand has a higher prevalence of nine of the 12 risk factors – including high rates of untreated hearing loss.

This study would provide novel data to understand the relationship between changes in both hearing sensitivity (hearing ability) and central auditory processing (listening ability), and brain structure in midlife – prior to the onset of clinical hearing loss or cognitive impairment. Additionally, it may shed light on the mechanisms underlying these associations. This focus on pre-clinical hearing changes is a new and emerging area and may identify early indicators and potentially personalised and modifiable factors to prevent the advancement of hearing loss and potential cognitive decline. It is critical to delay the onset of age-related illnesses in order to minimise the burden of disease on society.

References:

Bidelman, G. M., Lowther, J. E., Tak, S. H., & Alain, C. (2017). Mild Cognitive Impairment Is Characterized by Deficient Brainstem and Cortical Representations of Speech. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *37*(13), 3610–3620. https://doi.org/10.1523/JNEUROSCI.3700-16.2017

Brayne C. (2007). The elephant in the room - healthy brains in later life, epidemiology and public health. *Nature reviews. Neuroscience*, *8*(3), 233–239. https://doi.org/10.1038/nrn2091

Croll, P.H., Vernooij, M.W., Reid, R.I., Goedegebure, A., Power, M.C., Rigters, S.C., Sharrett, A.R., Baatenburg de Jong, R.J., Mosley, T.H., de Groot, M., Lin, F.R. & Deal, J.A. (2020). Hearing loss and microstructural integrity of the brain in a dementia-free older population. *Alzheimer's & Dementia, 16,* 1515-1523. DOI: 10.1002/alz.12151

Deary, I. J., Corley, J., Gow, A. J., Harris, S. E., Houlihan, L. M., Marioni, R. E., Penke, L., Rafnsson, S. B., & Starr, J. M. (2009). Age-associated cognitive decline. *British medical bulletin*, *92*, 135–152. https://doi.org/10.1093/bmb/ldp033

Elliott, M.L.; Caspi, A.; Houts, R.M.; Ambler, A.; Broadbent, J.M.; Hancox, R.J.; Harrington, H.; Hogan, S.; Keenan, R.; Knodt, A.; Leung, J.H.; Melzer, T.R.; Purdy, S.C.; Ramrakha, S.; Richmond-Rakerd, L.S.; Righarts, A.; Sugden, K.; Thomson, W.M.; Thorne, P.R.; Williams, B.S.; Wilson, G.; Hariri, A.R.; Poulton, R. & Moffitt, T.E. (2021). Disparities in the pace of biological aging among midlife adults of the same chronological age have implications for future frailty risk and policy. *Nature Aging*, *1,* 295-308. https://doi.org/10.1038/s43587-021-00044-4

Fan, Y.T., Fang, Y.W., Chen, Y.P., Leshikar, E.D., Lin, C.P., Tzeng, O.J.L., Huang, H.W. & Huang, C.M. (2019). Ageing, cognition, and the brain: Effects of age-related variation in white matter integrity on neuropsychological function. *Aging & Mental Health, 23*(7), 831-839. DOI: 10.1080/13607863.2018.1455804

Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, van der Kouwe A, Killiany R, Kennedy D, Klaveness S, Montillo A, Makris N, Rosen B, Dale AM. (2002). Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron, 33*(3):341-55. doi: 10.1016/s0896-6273(02)00569-x.

Glasser MF, Coalson TS, Robinson EC, Hacker CD, Harwell J, Yacoub E, Ugurbil K, Andersson J, Beckmann CF, Jenkinson M, Smith SM, Van Essen DC. (2016). A multi-modal parcellation of human cerebral cortex. *Nature, 536*(7615):171-178. doi: 10.1038/nature18933.

Ha, J., Cho, Y.S., Kim, S.J., Cho, S.H., Kim, J.P., Jung, Y.H., Jang, H., Shin, H.Y., Lin, F.R., Na, D.L., Seo, S.W., Moon, I.J. & Kim, H.J. (2020). Hearing loss is associated with cortical thinning in cognitively normal older adults. *European Journal of Neurology, 27,* 1003-1009. DOI:10.1111/ene.14195

Humes, L.E., Busey, T.A., Craig, J. & Kewley-Port, D. (2013). Are age-related changes in cognitive function driven by age-related changes in sensory processing? *Attention, Perception and Psychophysiology, 75*(3), 508-524.

Lemke, U., & Besser, J. (2016). Cognitive Load and Listening Effort: Concepts and Age-Related Considerations. *Ear and hearing*, *37 Suppl 1*, 77S–84S. https://doi.org/10.1097/AUD.0000000000000304

Lin, F.R., et al. (2013). Hearing loss and cognitive decline in older adults. *JAMA Intern Med,* 173(4), 293-9.

Lindenberger, U., & Baltes, P. B. (1994). Sensory functioning and intelligence in old age: A strong connection. *Psychology and Aging, 9*(3), 339-355. https://doi.org/10.1037/0882-7974.9.3.339

Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., Brayne, C., Burns, A., Cohen-Mansfield, J., Cooper, C., Costafreda, S.G., Dias, A., Fox, N., Gitlin, L.N., Howard, R., Kales, H.C., Kivimäki, M., Larson, E.B., Ogunniyi, A… Mukadam, N. (2020). Dementia prevention, intervention, and care: 2020 report of the *Lancet* Commission. *The Lancet Commission*. https://doi.org/10.1016/S0140-6736(20)30367-6

Manno, F.A.M., Rodriguez-Cruces, R., Kumar, R., Ratnanather, J.T. & Lau, C. (2021). Hearing loss impact gray and white matter across the lifespan: Systematic review, meta-analysis and meta-regression. *NeuroImage, 231*(117826). https://doi.org/10.1016/j.neuroimage.2021.117826

Ma'u, E., Cullum, S., Cheung, G., Livingston, G. & Mukadam, N. (2021). Differences in the potential for dementia prevention between major ethnic groups within one country: A cross sectional analysis of population attributable fraction of potentially modifiable risk factors in New Zealand. *The Lancet Regional Health – Western Pacific, 13*(100191), 1-9.

Peelle, J.E. & Wingfield, A. (2016). The neural consequences of age-related hearing loss. *Trends in Neurosciences, 39*(7), 486-497. http://dx.doi.org/10.1016/j.tins.2016.05.001

Profant, C., Škoch, A., Balogová, A., Tintěra, J., Hlinka, J. & Syka, J. (2014). Diffusion tensor imaging and MR morphometry of the central auditory pathway and auditory cortex in aging. *Neuroscience, 260,* 87-97. http://dx.doi.org/10.1016/j.neuroscience.2013.12.010

Rigters, S.C., Cremers, L.G.M., Ikram, M.A., van der Schroeff, M.P., de Groot, M., Roshchupkin, G.V., Niessen, W.J.N., Baatenburg de Jong, R.J., Goedegebure, A. & Vernooij, M.W. (2018). White-matter microstructure and hearing acuity in older adults: A population-based cross-sectional DTI study. *Neurobiology of Aging, 61,* 124-131. https://doi.org/10.1016/j.neurobiolaging.2017.09.018

Roberts, R., & Knopman, D. S. (2013). Classification and epidemiology of MCI. *Clinics in geriatric medicine*, *29*(4), 753–772. https://doi.org/10.1016/j.cger.2013.07.003

Spreng, R. N., Wojtowicz, M., & Grady, C. L. (2010). Reliable differences in brain activity between young and old adults: a quantitative meta-analysis across multiple cognitive domains. *Neuroscience and biobehavioral reviews*, *34*(8), 1178–1194. https://doi.org/10.1016/j.neubiorev.2010.01.009

Wakana S, Caprihan A, Panzenboeck MM, et al. (2007). Reproducibility of quantitative tractography methods applied to cerebral white matter. *Neuroimage, 36*(3):630-644. doi:10.1016/j.neuroimage.2007.02.049.

DATA SECURITY AGREEMENT

Provisional Paper Title	Hearing across the lifecourse and associated changes in the brain.
Proposing Author	Kirsten Cheyne
Today's Date	13/10/22

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

Please initial your agreement: (customize as necessary)

KRC	I am current on Human Subjects Training [CITI www.citigrogram.org] or equivalent.
KRC	My project is covered by the Dunedin Study's ethics approval OR I have /will obtain ethical approval from my home institution (please specify).
KRC	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.
KRC	I will not "sync" the data to a mobile device.
KRC	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).
KRC	I will not share the data with anyone, including my students or other collaborators not specifically listed on this concept paper.
KRC	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.*
KRC	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: