DUNEDIN STUDY CONCEPT PAPER FORM

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

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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.

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