**Concept Paper template form**

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| **Provisional Paper Title:** Midlife functional connectivity correlates of past environmental exposures |
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| **Today's Date:** 9/30/2025 |

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

**Objective of the project:**

Functional connectomics allows for the modeling of brain health as a system of dynamic changes in the networking of the brain (Contreras et al., 2015). This, in turn, offers new avenues to identify potential mechanisms of disease in the aging brain. As a new field of study, the connectome remains under-investigated with regards to putative risk factors for Alzheimer's disease (AD) and AD-related dementias (ADRD). We propose to advance the field of brain aging through a series of separate but related studies in the Dunedin Cohort that seek to connect the midlife brain connectome to past environmental exposures that putatively enhance ADRD risk, as identified in previously published studies in the cohort. In particular, the Dunedin Study is uniquely well-positioned to evaluate two important elements of the exposome—neighborhood socioeconomic disadvantage and childhood lead exposure.

Elevated risk for disease and premature mortality tends to follow socioeconomic gradients at both individual and area (neighborhood) levels in countries with and without robust social safety nets (Diez & Mair, 2010; Meijer et al., 2012; Baranyi et al., 2022), as recently reported in the Dunedin Cohort (Reuben et al., 2024). Lead, meanwhile, is a neurotoxicant in wide industrial and commercial use, with evidence increasingly suggesting that lead exposure across the lifespan may elevate risk for neurodegenerative disease in old age, particularly if the exposure occurs very early (Reuben 2018) or very late (Shih et al. 2007) in life, with notable enhancement of cognitive decline in the Dunendin Cohort (Reuben et al., 2020). Risks associated with exposure to lead and neighborhood disadvantage remains under characterized: dose-response associations for clinical outcomes, mechanisms of effect, factors that influence individual differences, and the dynamics of exposure timing and degeneration onset have not been established.
Prior work from the Dunedin Study has shown that both childhood lead exposure and neighborhood socioeconomic disadvantage are associated with signs of diminished structural brain integrity in midlife (Reuben et al. 2020; Reuben et al., 2024). However, it is unclear what, if any, functional connectivity patterns may underly or co-exist with these signs of impaired structural integrity. Brain function can be estimated using functional MRI

(fMRI) which measures changes in blood oxygenation of brain regions as a proxy for neural activity. Using fMRI, researchers can identify patterns of correlated activity in different brain regions and ultimately identify brain-wide networks of co-activity. This method is referred to as "functional connectivity." Compared to brain structure, functional connectivity measures are thought to be more closely linked to variation in behavior and cognition (Marek et al. 2022). As such, understanding the links between past environmental exposures and brain functional connectivity will help establish how exposure ultimately gives rise to cognitive deficits and, potentially, neurodegenerative disease.

Here, we propose to extend prior work in the Dunedin Study by testing associations of past environmental exposures (childhood lead and neighborhood socioeconomic disadvantage across adulthood) with midlife brain functional connectivity using a novel but previously published measure with good test-retest reliability derived from fMRI scans collected from Study members at age 45 (Elliott, 2019). We hypothesize that 1) Study members with a history of greater exposure to early life and later life neighborhood socioeconomic disadvantage will separately demonstrate differences in midlife brain functional connectivity when compared to those with lower exposure. These hypotheses are informed by findings that middle-aged Dunedin Study members with high childhood lead histories (Reuben et al. 2020) and neighborhood disadvantage in adulthood (Reuben et al. 2024) show diminished cognitive capacity relative to their peers, including lower full-scale IQ, greater decline in cognitive capacity from childhood, and greater reports of problems with everyday cognitive function.

After testing this primary hypothesis, we will then investigate follow-up questions including whether brain functional connectivity and exposome associations overlap with associations between brain functional connectivity and cognitive decline from childhood. Such an overlap would provide further evidence that the cognitive decline observed among Study members with high lead or neighborhood disadvantage exposure may have been driven by functional differences in the brain Lastly, we will test whether lead associations with brain functional connectivity overlap with canonical neurotransmitter systems that modulate neural activity and are thought to be uniquely affected by lead exposure (e.g., GABA, dopamine).

## Data analysis methods:

### Primary Analysis: Are adult neighborhood disadvantage and childhood lead exposure associated with midlife brain functional connectivity?

We will test this question by training two separate elastic-net regression models to estimate neighborhood socioeconomic disadvantage exposure and childhood lead exposure according to functional connectivity measures from 769 Study members at age 45 (N=564 Study members participating in the age 45 assessment phase have present childhood lead data). These functional connectivity estimates are derived from the Human Connectome Minimal Processing Pipeline, a well-established protocol for cleaning fMRI data and estimating functional connectivity across the brain. We will train these models using a 90/10 train/test split and 10-fold cross validation. The accuracy of these models will establish the overall strength of an association between neighborhood disadvantage, lead, and midlife brain functional connectivity.

Next, we will test which brain functional connections are most strongly associated with the pre-specified exposures. To do this, for each exposure, we will examine the relative feature importance (Haufe et al. 2014) of the functional connectivity measures used in the model. This will allow us to establish whether functional connections within or

between specific brain networks are especially related to adult neighborhood disadvantage or childhood lead exposure.

**Secondary Analysis 1: Are neighborhood disadvantage, childhood lead exposure, and cognitive decline associated with similar patterns of midlife brain functional connectivity?**

Next, we will generate two analogous models that predict cognitive decline using this same set of brain functional connectivity measures for 1) neighborhood disadvantage and 2) childhood lead exposure. By comparing these models, we will establish whether a similar pattern of midlife brain functional connectivity reflects both the specified exposures and cognitive decline. To do this, in two separate analyses, we will calculate feature importance scores for both models and test the magnitude of correlation between these scores (twice, once for neighborhood disadvantage and again for lead exposure). If our exposome measures and cognitive decline are each associated with the same pattern of midlife brain functional connectivity, this provides evidence that cognitive decline among Study members with neighborhood disadvantage or high childhood lead exposure could have been partly driven by effects of these exposures on the brain.

**Secondary Analysis 2: Is the pattern of childhood lead exposure and midlife brain functional connectivity associated with specific neurotransmitter systems?**

Finally, we will conduct an exploratory analysis testing whether associations between childhood lead exposure and midlife brain functional connectivity are especially concentrated among pathways of specific neurotransmitter systems. To do this, we will use our lead prediction model to calculate feature importance scores for each brain region. Specifically, we will take the average feature importance for each parcel. Next, we will use neuromaps (Markello et al. 2022) to test whether these associations overlap with canonical distributions of various neurotransmitters, including GABAergic and dopaminergic systems which animal models suggest are particularly vulnerable to lead. This will allow us to discern if childhood lead exposure uniquely impacts midlife brain functional connectivity along specific neurotransmitter pathways or if it confers distributed effects across the brain.

All tests will be examined in models adjusted for sex and, separately, stratified for sex. Covariate-adjusted tests will utilized previously identified covarites utilized in studies of lead and neighborhoods in the Dunedin cohort, including childhood socioeconomic status and maternal IQ (lead study) and adult socioeconomic status (neighborhood study). If space allows, sensitivity tests in the lead study will substitute young adult blood lead level (age 21) for childhood level to test potential specificity of timing effects regarding exposure.

**<u>Variables needed at which ages:</u>**

<u>Dunedin Study:</u>

- Outcome:
    - Glasser 360 general functional connectivity matrices from Phase 45 brain fMRI data
    - In-scanner head motion
- Exposure:
    - Childhood blood-lead level (age 11)
    - Young adult blood-lead level (age 21years)
    - Cumulative Neighborhood Disadvantage, ages 26 to 45 years (composite

variable created via factor analysis for Reuben et al., 20204, *Alzheimer's & Dementia*)

- Other:
    - Childhood full-scale IQ (age 7-9 composite)
    - Age 45 full-scale IQ and residuzalized IQ decline by age 45
    - Sex
    - Childhood socioeconomic status
    - Maternal IQ
    - Age 45 socioeconomci status

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

This will be the first study of these exposure phenotypes and midlife brain functional connectivity. This project will be of interest to the growing field of exposome implications for brain aging as well as the functional connectome.

**If using Dunedin study data: How the paper will contribute to Māori health advancement and/or equitable health outcomes**

Māori residents of New Zealand are more likely to live in neighborhoods ranked as socioeconomically deprived. Furthermore, contemporary lead exposure in Aotearoa New Zealand follows socioeconomic gradients such that individuals living in more disadvantaged urban areas, including Māori residents, may be exposed to lead disproportionately. Better understanding of the long-term neurological consequences of both neighborhood socioeconomic disadvantage and lead exposure will inform the development of interventions to reduce neurodegenerative disease and health disparities arising from lead exposure across the population.

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