DUNEDIN STUDY CONCEPT PAPER FORM

Provisional Paper Title: Childhood lead exposure and adult hippocampal subfield volumes

Proposing Author: Aaron Reuben & Annchen Knodt

Author's Email: aaron.reuben@duke.edu

P.I. Sponsor: Ahmad Hariri

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

Objective of the study:

Lead is a neurotoxicant in wide industrial and commercial use. Increasingly, evidence suggests that lead exposure across the lifespan may elevate risk for neurodegenerative disease in old age, particularly if the exposure occurs very early[1] or very late[2] in life. This risk 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.

In this regard, interactions of lead exposure with the structural integrity of the hippocampus has emerged as an important research focus due to the hippocampus's involvement in memory and Alzheimer's disease and an emerging evidence base which suggests that the hippocampus may have specific vulnerability to lead. In rodent models, low-level early life lead exposure has been linked to differential metabolism,[3] gene expression,[4] and diffusivity[5] in the hippocampus. Two observational studies of adults have identified smaller total hippocampal volumes and altered metabolism among adults occupationally exposed to lead.[6,7] While in our own investigations of lead exposure in the Dunedin Study we have reported smaller total hippocampal volumes among adults exposed to lead as children,[8] our evidence suggested that these lead-brain differences were not specific to the hippocampus. Among adult members of the Dunedin Study tested for lead exposure in childhood, higher childhood blood lead levels were associated with smaller subcortical brain region volumes in all regions examined (12 of 12), not just the hippocampus.

Two new studies, one in rodent models[9] and one investigating blood-lead levels among male workers in the smelting industry in Xi'an, China,[10] have recently suggested that lead exposure may selectively impair specific subfields of the hippocampus. If this is true, it would suggest that our earlier examination of total hippocampal volumes in relation to childhood lead

exposure may have masked differences at the subfield level – differences that may be relevant to understanding the pathogenicity of lead in the aging brain and specific cellular mechanisms that may be future targets for intervention. Notably, recent studies have suggested that hippocampal subfield volumes outperform total hippocampal volumes in clinical tasks, such as predicting conversion of patients with mild cognitive impairment to dementia.[11]

Here we propose to follow-up our 2020 JAMA paper[8] reporting lower total hippocampal volumes in adults exposed to lead with a limited investigation of the association of childhood blood lead levels with adult volumes of all 12 hippocampal subfields. Our goal will be to replicate the adult study from Xi'an, China, (Shi et al., 2023) which had an N of 49, using members of the Dunedin Study with past blood-lead levels and current brain imaging (N=565). This narrowly focused project will target the journal that published the Xi'an results, *Ecotoxicology and Environmental Safety*, as a short report.

Data analysis methods:

Using multiple linear regression, we will test the association of childhood blood lead levels with adult hippocampal subfield volumes, aiming to match the methods of Shi et al (2023). As with Shi et al., we will test subfield hemispheres separately. Tests of differences between dependent correlations[12] will be conducted to determine subfield-specific associations. Primary tests will adjust for sex statistically, given known sex differences in hippocampal volumes and lead levels, but follow-up tests may also investigate associations stratified by sex. Follow-up tests will investigate sex-adjusted associations additionally controlling for total hippocampal volume, as a most conservative approach to identifying subfield-specific associations. If space allows, tests may also include non-hippocampal subcortical regions to test for any hippocampus-specific associations with lead not previously reported in Reuben and Elliott et al (2020). Sensitivity tests may also apply additional covariate adjustments using the covariates utilized in Reuben and Elliott (maternal IQ and childhood socioeconomic status).

Variables needed at which ages:

- Sex
- Maternal IQ
- Childhood socioeconomic status
- Childhood blood-lead level (age 11 years)
- Adult MRI measures of
    - Total brain volume
    - All 12 cortical subregion volumes (including total hippocampal volume)
    - All 12 hippocampal subfields, separately by hemisphere

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

This project will be of interest to the evolving field of lead exposure implications for brain aging. It will also inform current research into the mechanisms and timing of lead-exposure associations with dementia.

References:

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