CONCEPT PAPER

Childhood lead exposure and adult brain aging

Provisional Paper Title: Childhood lead exposure and adult brain aging

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P.I. Sponsor: Terrie Moffitt, Avshalom Caspi

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Objective of the study:

Lead, a heavy metal able to substitute for calcium in the body, is known to cause diverse damage to the developing brain, including disrupting neuronal development, myelination, and neurochemical processing.[1] Lead exposed children consequently develop lower intellectual, fine motor skill and emotional regulation abilities than their less exposed peers, among other deficits.[2] The long-term consequences of childhood lead exposure remain poorly characterized, but, in one of the longest follow-ups to date on a cohort of lead exposed children, we reported that IQ deficits associated with childhood lead exposure were detectible in Dunedin Study members at midlife.[3] This finding extended previous work reporting cognitive impairment and brain abnormalities in young adults exposed to lead as children.[4–7] We also found that midlife IQ deficits represented decline from childhood IQ levels measured several years before lead-exposure was assessed.[3]

Cognitive deficits relative to peers and cognitive decline measured across many years represent profound risk factors for degenerative brain disease.[8–10] Dementia in particular appears to be preceded by several years of "progressively accelerating" cognitive decline.[8(p354)] It is not yet clear if cognitive decline associated with childhood lead exposure represents a risk factor for neurodegenerative disease, but evidence from animal studies, and one study of lead-exposed children, suggests that early-life lead exposures can condition the brain for accelerated aging via epigenetic changes related to over-expression of pathology-relevant proteins.[11–14] At least one study of lead-exposed children has reported similar epigenetic changes leading to over-expression of pathology-related proteins.[13] Lead exposure in adulthood, meanwhile, has been linked to accelerated cognitive decline in late-life and, at high levels, increased risk of neurodegenerative disease.[15,16] Childhood lead exposure represents a significant, largely unexplored, potential risk factor for neurodegenetative disease.[17]

If childhood lead exposure leads to greater adult neurodegenerative disease or altered rates of adult brain aging, the implications for public health would be significant. Millions of adults living in developed countries were historically exposed to high levels of lead as children [18], and millions of children living in developing countries still face high lead exposures [19–21].

This proposed study would seek to evaluate the hypothesis that individuals exposed to high levels of lead as children are at greater risk for neurodegenerative disease later in life as indicated, at age 45, by abnormalities in brain structure and functional connectivity suggestive of accelerated brain aging.[22–25]

<u>Data analysis methods:</u>

We will conduct two main categories of analysis:

Analysis 1: Investigating associations between childhood blood lead and adult brain structure.

Through correlations and multivariate regressions we will test the hypothesis that early life blood lead levels, measured at age 11 years, are related to abnormalities in adult brain structure indicative of accelerated brain aging, as measured through grey matter and white matter MRI measures. Our primary outcomes will be average cortical thickness, total surface area, average fractional anisotropy (FA), white matter hyperintensity volume, hippocampal volume, and Brain Age. Our secondary outcomes will assess whether there is regional specificity in the relationship between lead and brain structure differences, measured through regional cortical thickness, regional surface area, and tract-level FA. We will include potential confounds commonly included as covariates in studies of brain aging and health effects of lead exposure, including sex, childhood SES (average 1-15), childhood IQ, and maternal IQ. We will also include child head circumference (age 5) as a potential proxy measure of early life brain volume.

Analysis 2: Investigating associations between childhood blood lead and adult brain functional connectivity

An exploratory analysis will test the hypothesis that early life blood lead levels are related to measures of adult brain functional connectivity at age 45 years that are indicative of accelerated brain aging. We will perform a Connectome-Wide Association Study and will follow-up any significant results to probe for region-wide contributions to the main effect. We will include the same covariates selected for the primary analyses.

Additional tests

Following the two main analyses, we will conduct a third analysis, space permitting, investigating associations between childhood blood lead and adult brain function as represented by cognitive ability. This potential final analysis will test the functional / practical implications of childhood lead exposure's relationship to adult brain health and extend our previous findings on lead's relationship with IQ and cognitive decline. Through correlations and multivariate regressions we will test the hypothesis that early life blood lead levels will relate to lower adult IQ at age 45, downward change in IQ from age 7-9, and the presence of cognitive complaints. Covariates will include sex, childhood SES (average 1-15), and maternal IQ. Change in IQ will be tested using both residualized change and difference score approaches.

An important additional caveat is that lead exposure data are not available for all Dunedin Study members, so we will need to test for selective missingness, and to control for any possible selectivity in all analyses.

<u>Variables Needed at Which Ages (DUNEDIN STUDY):</u>

Predictors
Blood lead (uncorrected) at age 11

Outcomes
Brain Structure at age 45
- Grey matter measures
    - Cortical thickness – whole brain (primary) and regional (secondary)
    - Surface area – Whole brain (primary) and regional (secondary)
    - Subcortical volume – hippocampus (primary) all other (secondary)
- White matter measures
    - Fractional Anisotropy – voxel-wise whole brain (primary) and by tract (secondary)
    - White matter hyperintensity volume (primary)
- Brain age (primary)

Brain Function at age 45
- General Functional Connectivity (secondary)

Adult IQ & subscales at age 45
Informant and self-reported memory problems at age 45
Informant and self-reported attention problems at age 45

Covariates
sex
average SES 1-15
momiq3
Head circumference – age 5 HC05
IQ – age 7 & 9
ICV – age 45

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

Millions of adults living in developed countries were historically exposed to high levels of lead as children, and millions of children living in developing countries still face high lead exposures. If childhood blood lead levels are found to predict adult brain aging, it would suggest that persistent environmental toxins may play a greater role in the global prevalence of neurodegenerative disease and have a greater influence on life trajectories than previously assumed. Regardless of its findings, this study will hold implications for clinical practice and public health, particularly for decisions about the scope and duration of public responses to community lead exposure events. This study would also inform efforts to remove lead from the current environment, in both developed and developing countries.

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Data Security Agreement

Provisional Paper Title	Childhood lead exposure and adult brain aging
Proposing Author	Aaron Reuben and Maxwell Elliott
Today's Date	April 18th, 2019

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

_ASR I am current on Human Subjects Training (CITI (www.citiprogram.org) or equivalent)

_ASR My project is covered by Duke or Otago IRB OR I have /will obtain IRB approval from my home institution.

_ASR I will treat all data as "restricted" and store in a secure fashion.
My computer or laptop is: a) encrypted (recommended programs are FileVault2 for Macs, and Bitlocker for Windows machines) b) password-protected c) configured to lock-out after 15 minutes of inactivity AND d) has an antivirus client installed as well as being patched regularly.

_ASR I will not "sync" the data to a mobile device.

_ASR In the event that my laptop with data on it is lost, stolen or hacked, I will immediately contact Professor Moffitt or Caspi. (919-684-6758, tem11@duke.edu, ac115@duke.edu)

_ASR I will not share the data with anyone, including students or other collaborators not specifically listed on this concept paper.

_ASR 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 cannot be shared because the Study Members have not given informed consent for unrestricted open access. Speak to Terrie or Avshalom for strategies for dealing with data sharing requests from Journals.*

_ASR 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: ..../s/ Aaron Samuel Reuben...

CONCEPT PAPER RESPONSE FORM

A.

Provisional Paper Title	Childhood lead exposure and adult brain aging
Proposing Author	Aaron Reuben and Maxwell Elliott
Other Contributors	Terrie Moffitt, Avshalom Caspi, Ahmad Hariri, Annchen Knodt, Richie Poulton, Sandhya Ramrakha, Renate Houts, Jonathan Broadbent, David Ireland, Cliff Abrams
Potential Journals	JAMA Neurology, Neurology, Nature Neuroscience
Today's Date	April 18th, 2019
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B. To be completed by potential co-authors:

	Approved
	Not Approved
	Let's discuss, I have concerns

Comments:

Please check your contribution(s) for authorship:

	Conceptualizing and designing the longitudinal study
	Conceptualizing and collecting one or more variables
	Data collection
	Conceptualizing and designing this specific paper project
	Statistical analyses
	Writing
	Reviewing manuscript drafts
	Final approval before submission for publication
	Acknowledgment only, I will not be a co-author

Signature: