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HUMAN DEVELOPMENT, BIRTH TO DEATH

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Genes Environment Health Behavior

Concept Paper Form

Provisional Paper Title: Chronic inflammation and brain morphology in midlife
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P.I. Sponsor: Avshalom Caspi, Terrie Moffitt and Ahmad Hariri
Today's Date: 2/22/2020

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

Objective of the study:

- Chronic inflammation and biological aging are associated with age-related features of the brain.
- If CRP, IL-6, and suPAR are measures of chronic inflammation, we would expect them to predict individual differences in aging and health outcomes. Here, we expect that suPAR is the better measure of chronic inflammation.
- A previous study of 1800 older adults found associations between CRP and IL-6 with cross-sectional brain aging measures but did not find associations between baseline CRP and IL-6 and the evolution of MRI findings 4 years later[1]. Since CRP and IL-6 are acute-phase reactants[2,3], they may not necessarily capture chronic ongoing effects to the same extent as suPAR[4–6].
- Many studies of systemic inflammation and changes of the brain are done in older populations[1,7] (65+ years where you'd expect most to show advanced signs of aging) or in non-representative samples[8], e.g., often small clinical samples (depression, etc.) or overly healthy populations[9,10] (healthy community volunteers with many exclusion criteria). This limits our ability to understand the association of chronic inflammation, aging and health in the broader population.
- The Dunedin cohort is a population-representative and relatively large midlife cohort which will make an investigation of the association between CRP, IL-6 and suPAR and midlife brain aging particularly informative.
- **Main hypothesis:** Inflammation has deleterious effects on aging and the brain. We hypothesize that elevated CRP, IL-6 and suPAR will be associated with thinner cortex, smaller cortical surface area, larger white matter hyperintensity (WMH) volume,

decreased fractional anisotropy (FA), and smaller hippocampal volume. These brain morphological differences are all indicative of early signs of accelerated brain aging. If suPAR is a better measure of chronic inflammation than CRP and IL-6, we would expect suPAR to be more strongly associated with these signs of accelerated brain aging than CRP and IL-6.

Data analysis methods:

Primary analysis: (with additional sensitivity analyses controls for sex, BMI, smoking and, in analyses of suPAR, controls for CRP and IL-6)

- **Cross-sectional age 45 associations:** Between each inflammatory biomarker individually (CRP, IL-6, suPAR) with average measures of:
    - cortical thickness
    - surface area
    - WMH volume
    - hippocampal volume
    - fractional anisotropy

Secondary analyses:

- **Longitudinal associations between age 38 inflammation with age 45 brain:**
    - Associations between each inflammatory biomarker (measured at age 38) with cortical thickness, surface area, WMH volume, FA and hippocampal volume at age 45
    - Associations between each inflammatory biomarker (measured at age 38) with brain age gap estimate (brainAGE) at age 45
- **Cross-sectional age 45 associations**:
    - Parcel-wise associations between CRP, IL-6 and suPAR with SA and CT
    - Spatial correlations between parcel-wise maps of CRP, IL-6, and suPAR for associations with SA and CT
    - Average cortical volume (for comparisons with literature)
    - All other subcortical volume associations
    - Tract-wise FA associations in John Hopkins atlas
    - Brain age gap estimate (brainAGE)

NOTE: As brainAGE associations with suPAR have been reported in another manuscript, it is not considered a primary measure of this study; however, associations with CRP and IL-6 have not previously been reported.

Variables needed at which ages:

Brain Variables:

- *Average cortical thickness, surface area, hippocampal volume, WMH volume, FA and total cortical volume*
- *Parcel-wise cortical thickness and surface area*
- *All aseg subcortical volumes*
- *Brain-age and brainAGE*
- *Tract-wise FA for John Hopkins atlas*

Systemic inflammation:

- *CRP, IL-6, and suPAR at age 38 and 45*

Additional covariates:

- *Sex, BMI, current smoking status at 38 and 45*

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

- Aging is a lifelong process and there is increasing awareness that to best intervene on age-related diseases, interventions must be applied earlier in life. Chronic inflammation is thought of as a common pathway through which many different age-related diseases arise. Most studies of inflammation are in the wrong cohorts (too old or too ill) and with the wrong biomarkers (acute inflammation markers). In this study we have the potential to clarify whether links between systemic chronic inflammation and brain aging are already present in midlife in a population representative birth cohort.
- Chronic inflammation contributes to accelerated aging of the body. It is currently unknown to what extent aging of the body contributes to aging of the brain. This study will help us understand whether a known contributor to accelerated aging of the body (chronic inflammation) is associated with early signs of aging in the brain.
- By comparing widely used inflammation markers (CRP and IL-6) with a novel inflammation marker (suPAR) in a study of the brain in midlife adults, we hope to advance our knowledge of the extent to which each of these markers index systemic chronic inflammation.

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Data Security Agreement

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☒	I am current on Human Subjects Training (CITI (www.citiprogram.org) or equivalent)
☒	My project is covered by the Duke ethics committee OR I have /will obtain ethical approval from my home institution.
☒	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.
☒	I will not "sync" the data to a mobile device.
☒	In the event that my laptop with data on it is lost, stolen or hacked, I will immediately contact Moffitt or Caspi.
☒	I will not share the data with anyone, including my students or other collaborators not specifically listed on this concept paper.
☒	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. Study participants have not given informed consent for unrestricted open access, so we have a managed-access process. Speak to Temi or Avshalom for strategies for achieving compliance with data-sharing policies of journals.*
☒	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. This data remains the property of the Study and cannot be used for further analyses without an approved concept paper for new analyses.

Signature: Maxwell Elliott & Line Jee Hartmann Rasmussen