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HUMAN DEVELOPMENT, BIRTH TO DEATH

Moffitt & Caspi
Genes Environment Health Behavior

Provisional Paper Title: Is an unfair start in life, associated with high-need, high-cost health and social outcomes, observable in midlife structural brain integrity?
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Please describe your proposal in 2-3 pages with sufficient detail for helpful review.

Objective of the study:

Previous studies by our group have identified a high-need, high-cost segment of the Dunedin Study cohort, which although representing only approximately one-fifth of the cohort accounted for a majority of the burden across numerous health and social sectors (Caspi et al., 2016). This observation follows a well-known pattern termed the Pareto principle (Bunkley, 2008), which describes how only 20% of the population accounts for an average of 80% of the need and cost of services across multiple health and social sectors. In the Dunedin Study, this high-need, high-cost segment is characterized by a disadvantaged childhood, having lower childhood socioeconomic status (SES), IQ, and self-control as well as greater exposure to maltreatment (Caspi et al., 2016). This trend was observed even at the age of 3; individuals with poorer neurocognitive health experienced a greater number of high-need, high-cost health and social outcomes (Caspi et al., 2016; Richmond-Rakerd et al., 2020). Additionally, health and social problems tended to aggregate within the same individuals, who tended to have poorer mental health in early life (Richmond-Rakerd et al., 2020). This evidence indicates that individuals with an unfair start in life have an outsized burden of health and social problems, with deficits in a number of domains including mental health and cognitive functioning. The deficits experienced by these individuals bode poorly for their trajectory of aging. Recently, we have demonstrated that MRI-derived measures of structural brain integrity in midlife reflect the burden of lifetime mental illness as well as cognitive decline from childhood. Moreover, these MRI-measures may be useful early biomarkers of later accelerated cognitive decline and risk for Alzheimer's disease and related dementias (ADRD) (Elliott et al., 2019).

Here, we propose to investigate associations between these MRI-derived measures of midlife structural brain integrity and membership in the high-cost outcome group of the Dunedin Study. Specifically, we will examine data from over 800 Study members to test the hypothesis that Study members in the high-cost group will evidence poorer structural brain integrity associated with

accelerated cognitive decline and increased risk for ADRD (e.g., thinner cortex, smaller surface area, higher volume of WMH, reduced FA, older brainAGE, and smaller hippocampal volume). Furthermore, we will investigate the role of early childhood risk factors in the relationship between brain structure and high-need, high-cost group membership. Specifically, we will test whether early life disadvantage, as measured by childhood cognitive ability, social class, low self-control, and exposure to maltreatment, accounts for the structural differences observable for those in high-need, high-cost groups at midlife. Consistent with a call by Falk et al. (2020), this proposal will bring together neuroscience and epidemiology by using data from a large, population-representative cohort to generate accurate estimates of midlife structural brain integrity amongst high-cost outcome individuals, which will help inform their longer-term trajectories of aging and continued burden on society.

Data analysis methods:

To better understand our data, we will first examine the bivariate associations between our age-45 brain MRI measures, the number of high-cost groups to which the individual belongs, and covariates such as social class and childhood neurocognitive health (for more information about these variables, see "Variables needed at which ages" below).

Our primary analyses will consist of estimating OLS regression models to test associations between membership in high-cost outcome groups and age-45 brain MRI measures and while controlling for sex. We will correct for multiple comparisons across the global measures using a false discovery rate (FDR) procedure (Benjamini & Hochberg, 1995).

To characterize the spatial distribution of the associations between the cortical measures and high-cost group membership, we will conduct a secondary set of analyses of associations between parcel-wise SA and CT and high-cost group membership while controlling for sex. We will correct for multiple comparisons across each set of regional tests performed (i.e., CT, SA) by using a false discovery rate (FDR) procedure (Benjamini & Hochberg, 1995).

Next, we will determine whether individuals in a greater number of high-cost groups have altered macroscale cortical organization. Non-linear decomposition of individual functional connectivity matrices generates a principal cortical gradient that situates parcels along a hierarchy situating unimodal association cortex on one end and transmodal association cortex on the other. This cortical gradient is reflective of the fundamental structural and functional hierarchical organization of the brain. We will estimate an OLS regression model to test associations between a summary measure of the distance between each subject's unimodal and transmodal regions and high-cost group membership, controlling for sex.

To determine whether these associations are attributable to inequities in early life, we will covary for childhood factors that predict high-need, high-cost group membership, including childhood IQ, childhood social class, childhood self-control, and childhood maltreatment (Caspi et al., 2016). If the observed associations are attenuated, it suggests that the same factors predicting high-need, high-cost health and social outcomes in childhood are accountable for structural differences in the brain. If these associations remain significant after the inclusion of early childhood factors, it suggests that the processes affecting brain structure for individuals in high-need, high-cost groups are not fully captured by an unfair start in life, and likely continue across the lifespan.

Finally, we will conduct several post hoc sensitivity analyses to probe the robustness of the associations between midlife brain structure and high-cost group membership. First, we will investigate associations between high-cost outcome group membership and hippocampal volume and while covarying for total intracranial volume. This will allow us to determine whether high-cost group membership is associated with larger- or smaller-than-expected hippocampal volumes. Second, we will test whether the magnitude of associations differ based on the type of health or social outcome experienced by conducting a leave-one-out analysis, in which we will remove individual items from the high-cost group membership variable in turn.

Variables needed at which ages:

Primary Independent Variables:

Pareto Group (Pareto5_0to3, from Richmond-Rakerd et al., 2020): High-cost group membership is equal to the number of outcome categories for which an individual was considered part of the high-cost group (part of the 20% that accounted for a disproportionate share of the costs in that sector). The 5 outcome categories included: social welfare benefits, public hospital nights, prescription drug fills, injury insurance claims, and criminal convictions. Individuals who were members of more than 3 high-cost outcome groups were assigned to a 3+ category.

Primary Dependent Variables:

- **brainAge45Liem_ctrd**: brainAge, re-centered so that the mean matches the chronological mean. We generated brainAGE scores using a recently-published, publicly-available algorithm stacked algorithm to predict chronological age from vertex-wise cortical thickness and surface area data extracted from fsaverage4 standard space as well as subcortical volume extracted from the aseg parcellation (Liem et al., 2017; Elliott et al., 2019). Test-retest reliability was assessed in 20 Dunedin Study members (mean interval between scans=79 days). The ICC was .81, indicating excellent reliability.
- **img_WMHvol_whlBrain_lg45 (mm^3):** Log-transformed volume of white matter hyperintensities (WMH), or lesions in white matter that are detectable using fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging. WMHs were extracted from these images using an Unidentified Bright Object (UBO) Detector pipeline (Jiang et al., 2018). WMHs can have a number of causes, and therefore serve as a less specific marker of neurodegeneration than PSMD (Low et al., 2020). They are considered a marker of brain frailty and have been associated with cognitive and emotional dysfunction. The ICC was .87, indicating excellent reliability.
- **Global average Fractional Anisotropy (FA)** is a summary statistic of the primary parameters obtained from DTI--three eigenvalues that characterize the magnitude of the diffusivities parallel and perpendicular to the axonal fiber. Global FA represents the variance of the diffusion magnitude in these directions and represents microstructural integrity across the entire brain. The ICC was .96, indicating excellent reliability.
- **img_SA_TOT45 (mm^2):** Total cortical surface area across the entire brain. The ICC was .99, indicating excellent reliability.
    - **SA_*Glasser parcel* (360):** parcel-wise (Glasser et al., 2016) total surface area
- **corrCT_TOT (mm):** Average thickness of the cortical sheet across the entire brain, corrected for curvature and with medial wall removed) for each subject. The ICC was .85, indicating

excellent reliability.
    - **corrCT_*Glasser parcel* (360):** parcel-wise (Glasser et al., 2016) average cortical thickness
- **Hippocampal Volume (mm^3):** For each individual, volume of the hippocampus was derived from the Freesurfer "aseg" parcellation. As we have no prior hypotheses regarding differences in volume across the right and left hemispheres, R and L hemisphere hippocampal volumes will be averaged. The ICC was .98, indicating excellent reliability.
- **Hierarchical cortical gradient range (average transmodal parcel value – average unimodal parcel value):** The principal cortical gradient describing the greatest amount of variation in intrinsic connectivity (Margulies et al., 2016). This gradient captures the fundamental structural and functional hierarchical organization of the brain, situating unimodal cortical regions, such as primary sensory and motor cortex, at one end, and transmodal regions, such as regions within the default mode and frontoparietal networks, at the other. Individual gradients were derived via a non-linear dimensionality reduction of individual intrinsic functional connectivity data, and a summary metric was obtained by taking the average transmodal parcel values and subtracting the average unimodal parcel values. This summary metric may represent the extent to which an individual's motor and sensory processes are removed from higher-order, abstract processing.

Covariates:

- **Total Intracranial Volume (mm^3):** Added into our regression models to examine associations between the relative volume of the hippocampus and high-need, high-cost group membership. The ICC for total intracranial volume was .99, indicating excellent reliability.
- **Childhood Socioeconomic Status (SES):** Assessed with a six-point scale assessing parents' occupational status, categorized based upon the educational levels and income associated with that occupation in data from the New Zealand census (Elley & Irving, 1976).
- **Childhood IQ:** Assessed with the Wechsler Intelligence Scale for Children – Revised (WISC-R) administered at ages 7, 9, and 11 years. IQ scores for the three ages were averaged and standardized (Moffitt et al., 2011).
- **Childhood low self-control:** Assessed using nine measures of self-control: observational ratings of children's lack of control (ages 3 and 5 years) and parent, teacher, and self-reports of hyperactivity, lack of persistence, inattention, impulsive aggression and impulsivity (ages 5, 7, 9, and 11 years). Principal components analysis was conducted on these positively correlated measures and were averaged into a single composite (Moffitt et al., 2011).
- **Childhood maltreatment:** A cumulative index of the number of maltreatment indicators during the first decade of life. Maltreatment indicators include evidence of maternal rejection assessed at age 3 years by observational ratings of mothers' interaction with the study children, harsh discipline assessed at ages 7 and 9 years by parental report of disciplinary behaviors, 2 or more changes in the child's primary caregiver, and physical and sexual abuse reported by study members once they reached adulthood (Caspi et al., 2002). Following the example set by Caspi et al., 2016, we grouped together those individuals with more than two indicators of maltreatment.

<u>Significance of the Study (for theory, research methods or clinical practice)</u>:

Past research has demonstrated that there is a segment of the population that experiences an

outsized burden of high-cost health and social outcomes, and that this segment of the population experienced disadvantages in early life: low SES, the presence of childhood maltreatment, low self-control and cognitive functioning throughout development. This study aims to determine whether the disadvantages associated with high-need, high-cost group membership include reduced structural brain integrity in midlife, and to what extent the differences in brain structure can be accounted for by an unfair start in life. The findings from this study have important implications for the aging trajectories of those in the high-need, high-cost segment of the population, and may provide important insights for developing effective programs for the prevention of the disproportionate negative health and social outcomes experienced by this group.

Characterizing the brain structure of high-need, high-cost individuals at midlife is important, as differences in age-45 structural brain integrity measures could represent early biomarkers of later accelerated cognitive decline and risk for ADRD. Thus, the presence of these biomarkers may not only reflect current negative health and social outcomes, but also indicate future disadvantage during the aging process. Using a relatively large and population-representative sample will afford adequate power to conduct generate accurate estimates of midlife structural brain integrity amongst high-cost individuals, which will help inform their longer-term trajectories of aging. These findings could inform future research that will be required for policymakers and clinicians to fund and develop interventions to slow cognitive decline and buffer risk for ADRD that can provide a high return on investment.

Furthermore, understanding the links between childhood risk factors, midlife brain structural integrity, and high-need, high-cost outcomes may illuminate promising windows for intervention. If, for example, differences in brain structural integrity for those in high-need, high-cost groups are accounted for by early childhood risk factors, it may indicate that the processes underlying these associations may occur early in life. Thus, interventions efforts should prioritize the first decade of life to be maximally beneficial. If, however, structural differences are not accounted for by early childhood risk factors, the processes underlying these associations may be more protracted, and interventions may be most effective if they are developed with long-term usage in mind and include individuals across the life course. In either case, it would be well worth the effort to invest in efforts to assist with, or prevent, the experience of high-cost health and social outcomes and the associated reduction in brain structural integrity. Individuals in multiple high-need, high-cost groups often interface with numerous health and social services, many of them through the government. Therefore, governmental policies may be especially suited to reach this group, and provide the maximum payoff for both these individuals, and society as a whole.

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