GROWUPGROWOLD
HUMAN DEVELOPMENT, BIRTH TO DEATH

Moffitt & Caspi
Genes Environment Health Behavior

Concept Paper template form

Provisional Paper Title: How is childhood adversity related to midlife brain function and connectivity?
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Today's Date: 11/5/2025

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

Objective of the project:

The experience of adversity early in life increases risk for later developing psychopathology, especially internalizing disorders like depression (Green et al., 2009; Nanni, et al., 2012). Such risk may be mediated by effects of early life adversity on the structural and functional development of brain networks supporting cognition and emotion. We previously reported that Dunedin Study members who experienced adverse childhood experiences (ACEs)—both prospectively and retrospectively ascertained—had diminished midlife structural integrity of widely-distributed brain networks (Gehred et al., 2021). However, we have yet to investigate how ACEs may be reflected in the integrity of functional brain networks. A recent study reported that current and future symptoms of depression, which are common across internalizing disorders, map onto the relative expansion of a functional frontostriatal salience brain network that supports goal-directed behaviors, motivation, positive affect, and resilience to stress (Lynch et al., 2024). Motivated by this finding, here we propose to extend our structural brain findings in the Dunedin Study by testing if ACEs are reflected in a similar expansion of this *functional* brain network in midlife. In doing so, we can provide a novel mechanistic link between early life adversity and later life psychopathology that may inform the search for more effective treatment and prevention strategies.

Aim 1. Map prospectively measured ACEs onto relative expansion of the frontostriatal salience network. At the age 45 assessment, 93% of active Study members (N=875) completed an MRI scanning protocol. 769 of these Study members have 27 minutes of functional MRI (fMRI) data after quality control procedures, which allows for reliable estimates of brain network size (Elliott et al., 2019; Whitman et al., 2023). We will apply the InfoMap community detection algorithm, originally developed by Rosvall and Bergstrom (2008), to this fMRI data and generate maps of the frontostriatal salience network linked with depression by Lynch et al. We will then test the hypothesis that expansion of this network occurs in Study members who experienced more ACEs. We define "expansion" as the percentage of total cortical surface assigned to a specific functional network. As a test of specificity, we will determine if ACEs are associated with similar expansion of other

functional brain networks (e.g., Frontoparietal, Dorsal Attention, Somato-Cognitive-Action).

Aim 2. Map retrospectively measured ACEs onto relative expansion of the frontostriatal salience network. We will repeat the analyses from Aim 1 using retrospectively ascertained instead of prospectively ascertained ACEs. Consistent with an emerging literature (Reuben et al., 2017; Danese & Widom, 2020), our prior study of brain structural integrity (an objectively-measured outcome) found larger effect sizes for prospectively ascertained ACEs in comparison with retrospectively ascertained ACEs (Gehred et al., 2021). However, the overall pattern between prospectively and retrospectively ascertained ACEs was very similar. We hypothesize that this will be true for functional brain networks as well. Importantly, reporting associations with retrospectively ascertained ACEs would support critical replication efforts in other datasets, the majority of which do not include prospectively ascertained measures of early adversity (Baldwin, Reuben, & Newbury, 2019).

Aim 3. Map internalizing psychopathology onto relative expansion of the frontostriatal salience network. We will map internalizing psychopathology, as represented by Internalizing factor scores from our hierarchical model of psychopathology (Caspi et al., 2014), onto the relative expansion of the frontostriatal salience network. This will serve two purposes. First, it will serve as a conceptual replication effort of the findings reported by Lynch et al. (2024). Second, and more importantly, it will allow us to determine the overlap between possible patterns of network expansion associated with ACEs and that with internalizing psychopathology. The greater the degree of overlap, the more support that early life adversity may shape later risk for internalizing disorders through differences in this brain functional network. We will further conduct analyses of specificity by mapping Externalizing, Thought disorder, and general psychopathology (i.e., p) factor scores onto variation in the frontoparietal salience network. We will also map all four factors (internalizing, externalizing, thought disorder, and p) onto the other functional networks to examine the extent of observed associations to any specific network.

Data analysis methods:

We will test the hypotheses outlined in Aims 1 and 2 using ordinary least squares (OLS) regression, controlling for sex. Additionally, we will examine whether the association between ACEs and salience network size differs by sex. For Aim 3, we will develop a predictive model to determine whether the characteristics of vertex-level measures within the salience network can predict an individual's ACE score and their Internalizing factor score.

Variables needed at which ages:

Sex
RetroACEs ACEs retrospective_1June2015
RetroACEs_trunc ACEs retrospective, 4+ = 4, 1June 2015
ProACEs Prospective ACEs scale
ProACEs_trunc Prospective ACES, 4 or more = 4, 20 April 2015

Phase 45:
General Functional Connectivity (GFC) matrices
p factor scores
Internalizing factor scores
Externalizing factor scores

Thought disorder factor scores

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

Together, these three aims can deepen our understanding of how experiencing adverse events in childhood maps onto later differences in the organization of functional brain networks. The results may also clarify how functional network differences associated with ACEs intersect with those underlying psychopathology. In addition, the analyses provide a valuable opportunity to replicate and build upon the findings reported by Lynch et al. (2024).

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

This study will not include separate analysis of specific ethnic groups, but the results are expected to be generalizable to the Māori community. Childhood adversity is disproportionately present in socio-economically disadvantaged communities and an improved understanding of their impact on the brain will provide meaningful insight to support those most affected.

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