

## Concept Paper Template

**Provisional Paper Title:** Adult neural outcomes of adverse childhood events, both retrospectively and prospectively

**Proposing Author:** Madeline Farber

**Author's Email:** madeline.farber@duke.edu

**P.I. Sponsor:** Ahmad Hariri  
(if the proposing author is a student or colleague of an original PI)

**Today's Date:** July 5, 2018

---

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

### **Objective of the study:**

The quality of caregiving during early childhood is instrumental in determining brain development and associated clinical outcomes (1-4). Given the highly plastic nature of the developing brain, early experiences are often considered more impactful than later experiences (1, 3). Adverse childhood experiences (ACEs) are no exception; exposure to abuse, neglect, and trauma in early childhood are understood to have lasting negative effects on brain development over time (1-4). Growing recognition that childhood adversity negatively impacts long-term health and development is evidenced by the widespread adoption and administration of the Adverse Childhood Experience (ACE) module, provided by the US Center for Disease Control (CDC) (5). Despite this growing recognition, no studies to date have investigated (a) whether neurodevelopmental effects of ACEs last into adulthood, and (b) whether retrospective and prospective reports of ACEs are differentially associated with neural outcomes.

Here, we propose to address these limitations by examining associations between adverse childhood experiences and the structure, function, and connectivity of the brain in the Dunedin Multidisciplinary Health and Development Study. The neuroimaging portion of the "Dunedin Study" examines 4 neural hubs each coordinating information processing through a distributed circuitry supporting 4 behavioral capacities. For this Concept Paper, we will primarily focus on (a) limbic system circuitry through the amygdala hub and (b) whole-brain functional connectivity. Alterations in limbic system structure, function, and functional connectivity have been previously reported in individuals with exposed to early trauma, abuse, and neglect (6). We seek to leverage the unique nature of the "Dunedin Study" to explore how adverse childhood experiences are associated with neural structure and function in mid-life.

### **Data analysis methods:**

A series of analyses will be conducted investigating associations between childhood adversity and neural structure and function in mid-life. Analyses detailed below will be conducted using both prospective and retrospective ACEs reports (7), comparatively.

1. Bivariate correlations of ACEs and amygdala structure as indexed by grey matter volume (GMV)
2. Bivariate correlations of ACEs and amygdala function as indexed by threat-related reactivity
3. Associations of ACEs with limbic system circuitry as indexed by psychophysiological

- interaction (PPI) during threat processing
4. Associations of ACEs with distributed patterns of network intrinsic connectivity as indexed by general functional connectivity (GFC)

Following these primary analyses, we will conduct exploratory analyses investigating associations of ACEs with task-based neural function outside of the context of threat. The extant literature on childhood adversity has justifiably focused on the limbic system within threat processing. However, childhood adversity is also thought to be linked to mental illness broadly, which we cannot confidently confine to any specific brain region(s). As such, in addition to our primary focus on threat, we will also conduct exploratory whole-brain analyses during fMRI tasks probing executive function, reward processing, and memory.

#### **Variables needed at which ages:**

Primary measures of interest:

ACES, prospective – composite of ages 3, 5, 7, 9, 11, 13, 15

*This measure is pre-existing and has been previously reported by Reuben et al. (2016).*

ACES, retrospective – adulthood

*This measure is pre-existing and has been previously reported by Reuben et al. (2016).*

Neuroimaging variables (in house) – P45

Depending on our primary analyses, we may further investigate specific contributions of ACEs independent of covariates such as socioeconomic status, stressful life events, and study member diagnoses in childhood and/or adulthood, among others.

Additionally, depending on these findings, it may be beneficial to conduct post hoc analyses exploring the role of specific family environment variables (e.g. negative parenting and positive parenting in childhood and adolescence).

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

Past research examining associations of adverse childhood effects with brain development has been limited to (a) cross-sectional data or limited time windows, and (b) largely retrospective reports. To our knowledge, no studies have tested whether previously reported neural effects of childhood adversity extend into adulthood and whether effects of retrospectively reported ACEs match those reported prospectively. In the proposed study, we will utilize the unique nature of the Dunedin Study to explore neural outcomes of childhood adversity across the lifespan.

#### **References cited:**

1. McCrory E, De Brito SA, Viding E: Research review: the neurobiology and genetics of maltreatment and adversity. *J Child Psychol Psychiatry* 2010; 51:1079–1095 3.
2. Danese, A., Moffitt, T. E., Arseneault, L., Bleiberg, B. A., Dinardo, P. B., Gandelman, S. B., ... & Caspi, A. (2016). The origins of cognitive deficits in victimized children: implications for neuroscientists and clinicians. *American journal of psychiatry*, 174(4), 349-361.
3. Tottenham, N. (2014). The importance of early experiences for neuro-affective development. *Current Topics of Behavioral Neuroscience*, 16, 109-129. doi:10.1007/7854\_2013\_254

4. Tottenham, N. (2018). The Fundamental Role of Early Environments to Developing an Emotionally Healthy Brain. *Policy Insights from the Behavioral and Brain Sciences*, 5(1), 98-103.
5. Austin, A.E., & Herrick, H.W.B. (2014, May). The effect of Adverse Childhood Experiences on adult health: 2012 North Carolina Behavioral Risk Factor Surveillance System Survey. North Carolina State Center for Health Statistics Study No. 167, 1-15.
6. Tottenham, N., & Gabard-Durnam, L. J. (2017). The developing amygdala: A student of the world and a teacher of the cortex. *Current Opinion in Psychology*, 17, 55-60. doi:10.1016/j.copsyc.2017.06.012
7. Reuben A, Moffitt TE, Caspi A, Belsky DW, Harrington HL, Schroeder F, Hogan S, Ramrakha S, Poulton R, Danese A. (2016). *Journal of Child Psychology and Psychiatry* 57: 1103-1112

## Data Security Agreement

Provisional Paper Title	Adult neural outcomes of adverse childhood events, both retrospectively and prospectively
Proposing Author	Madeline Farber
Today's Date	July 5, 2018

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

Please initial your agreement

MF	I am current on Human Subjects Training (CITI ( <a href="http://www.citiprogram.org">www.citiprogram.org</a> ) or equivalent)
MF	My project is covered by Duke or Otago ethics committee OR I have /will obtain ethical approval from my home institution.
MF	<p>I will treat all data as "restricted" and store in a secure fashion.            My computer or laptop is:</p> <ul style="list-style-type: none"> <li>a) encrypted (recommended programs are FileVault2 for Macs, and Bitlocker for Windows machines)</li> <li>b) password-protected</li> <li>c) configured to lock-out after 15 minutes of inactivity AND</li> <li>d) has an antivirus client installed as well as being patched regularly.</li> </ul>
MF	I will not "sync" the data to a mobile device.
MF	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, <a href="mailto:tem11@duke.edu">tem11@duke.edu</a> , <a href="mailto:ac115@duke.edu">ac115@duke.edu</a> )
MF	I will not share the data with anyone, including my students or other collaborators not specifically listed on this concept paper.
MF	<p>I will not post data online or submit the data file to a journal for them to post.</p> <p><i>Some journals are now requesting the data file as part of the manuscript submission process. The Dunedin Study Members have not given informed consent for unrestricted open access, so we have a managed-access process. Speak to Terrie or Avshalom for strategies for achieving compliance with data-sharing policies of journals.</i></p>
MF	<p>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.</p> <p>The data remains the property of the Study and cannot be used for further analyses without an approved concept paper for new analyses.</p>

**Signature:** Madeline Farber

## CONCEPT PAPER RESPONSE FORM

### A

Provisional Paper Title	Adult neural outcomes of adverse childhood events, both retrospectively and prospectively
Proposing Author	Madeline Farber
Other Contributors	Ahmad Hariri, Terrie Moffitt, Avshalom Caspi, Richie Poulton, Sandhya Ramrakha, David Ireland, Tracy Melzer, Ross Keenan, Annchen Knodt
Potential Journals	Proceedings of the National Academy of Sciences, Biological Psychiatry, Developmental Cognitive Neuroscience
Today's Date	July 2, 2018
Intended Submission Date	Following Phase 45 data collection

***Please keep one copy for your records and return one to the proposing author***

### B. To be completed by potential co-authors:

<input type="checkbox"/>	Approved
<input type="checkbox"/>	Not Approved
<input type="checkbox"/>	Let's discuss, I have concerns

Comments:

Please check your contribution(s) for authorship:

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

**Signature:**

