

**PROGRESS REPORT 3**  
**Katie McLaughlin, PhD**  
**AIM for Mental Health/One Mind Rising Star Award**

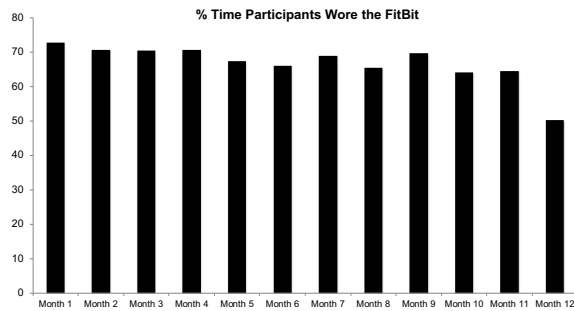
**1. Expenses**

There have been no major changes in the way the budget was used from the proposed initial budget.

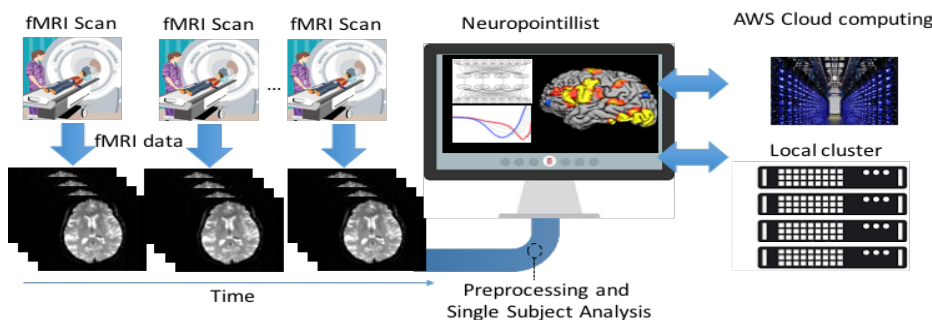
**2. Activities and Progress**

I have made tremendous progress on the study since the funding began in December, 2015. At this point, data collection for the study is complete and we have begun to analyze data. Major accomplishments over the past year include:

*Completion of Data Collection.* We enrolled a total of 30 adolescents in the study, each of whom was assessed monthly for an entire year, producing a total of 360 possible assessments. Of these, only 5 study visits were missed, producing an attendance rate of **97.3%**. Participants provided monthly data on stress exposure, mental health, brain structure and function (including both task-based and resting state fMRI), and social and emotional processes. In addition, continuous passively collected data on activity, sleep, and social behavior was acquired using participant smartphones and a FitBit that was given to each participant. Compliance with this protocol was excellent (see below for proportion of time spent wearing the FitBit). Data collection was finished in May, 2018 and the data have been cleaned and pre-processed. Data analysis is underway, and the results of our first major paper from this dataset have emerged (see below for details).



*Development of Software Tool to Analyze Longitudinal fMRI Data.* We developed an R package **Neuropointillist** that allows any model that can be specified in R to be estimated in fMRI data in each voxel of the brain. This affords complete flexibility to evaluate any statistical model of interest for voxel-wise fMRI analysis, including longitudinal models (e.g. SEM-based growth models). Such models cannot be estimated in existing fMRI software packages, limiting the inferences that can be made in longitudinal studies. Neuropointillist uses longitudinal fMRI data sets that have been preprocessed and creates a 2D surface cortical representation in a triangular mesh format (as supported by FreeSurfer) of person-level statistics and 3D representations of subcortical structures. Covariates and information about functional or structural connectivity between voxels or cortical parcels can also be input to the package. Neuropointillist accepts a model to be executed on each voxel in the dataset, written as a function called from R, and subdivides the dataset for parallel execution either on a custom architecture created using Amazon Web Services (AWS), or on a local cluster. The ability to divide the data into groups of voxels (e.g., based on spatial location or patterns of connectivity) ensures that a model can access the local voxel neighborhood, allowing the incorporation of neurobiological information that can be used to determine model fit across groups of voxels. Neuropointillist was used to analyze the fMRI data collected as part of the study (see below for results). We have made the software freely available (<http://github.com/IBIC/neuropointillist>) and have a paper in press describing the tool and its application to developmental neuroimaging studies:



Madhyastha, T. M., Peverill, M., Koh, N., McCabe, C., Flourney, J., Mills, K. L., . . . McLaughlin, K. A. (in press). Current methods and limitations for longitudinal fMRI analysis across development. *Developmental Cognitive Neuroscience*.

### 3. Major Findings

This study is the first to examine whether monthly variation in exposure to stressful life events is associated with within-person changes in brain activity in response to aversive and appetitive cues. Prior research has relied on between-person approaches that compare individuals with higher average levels of stress exposure to individuals with lower average levels of exposure. Here, we are able to examine whether changes in brain activity occur on months when adolescents experience more stress *than is typical for them*. These types of within-person effects of stress on brain function have never before been studied in humans. Indeed, we found that monthly variation in exposure to stressful life events was associated with neural responses to emotional cues in conservative, whole-brain cluster-corrected analyses.

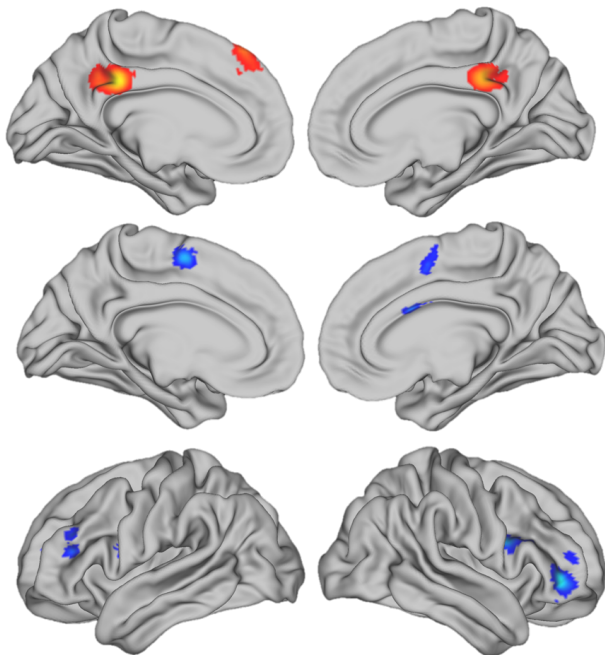
First, we examined between-person effects (i.e., do adolescents with higher average levels of stressful life events across the year exhibit differences in brain response to emotional cues than adolescents with low levels of stress). Here, we replicate prior work using a between-person approach. Adolescents with higher average levels of stress exhibited greater activation in multiple nodes of the salience network (i.e., thalamus, putamen) in response to aversive cues as well as the ventral visual stream (i.e., fusiform gyrus) than adolescents with lower average levels of stress.



Increased salience network activity in response to aversive cues among adolescents with higher average levels of stress

Second, in addition to this between-subjects effect, we find significant **within-person** associations of stressful life events with neural responses to aversive cues. These within-person effects occur in different regions of the brain than between-person effects.

Specifically, we find increased activity in the default mode network (i.e., posterior cingulate cortex) and reduced activity in the fronto-parietal network (middle frontal gyrus, inferior frontal gyrus, and dorsal anterior cingulate cortex) on months when adolescents reported greater exposure to stressful life events *than was typical for them*. To my knowledge, these types of within-subject associations between stressful life events and neural activity have never previously been documented. These findings demonstrate within-subject variability over time in neural responses to emotional cues in adolescence, and provide clear evidence that stressful life events play a meaningful role in shaping this variability. We demonstrate within-person effects in response to aversive cues not only in the salience network, where cross-sectional studies frequently report associations of stressful life events with neural activity, but also in the default mode network and fronto-parietal network, where between-person studies rarely observe stress effects in emotional processing tasks. These findings provide strong support for the central premise of the research project—that stressful life events dynamically shape brain activity during adolescence and are associated with **rapid changes** in neural responses to emotional stimuli. They further demonstrate that longitudinal, within-person designs have the power to reveal associations that are not typically observed in cross-sectional, between-person approaches.



Increased salience network activity and reduced activity in the fronto-parietal network in response to aversive cues on months when adolescents experienced greater exposure to stress *than was typical for them* (i.e., a within-person effect)

Finally, we observed that reduced activity in the fronto-parietal network in response to aversive cues was associated with increases in symptoms of depression and social anxiety **the following month**, demonstrating

that these stress-induced changes in the brain are a potential mechanism linking stressful life events with the onset of depression and anxiety during adolescence.

We are currently writing these findings up for publication.

#### 4. Publications

Although data collection is still underway, I have written multiple conceptual and methodological papers related to the project. I have published **78 papers** since the award began in December, 2015. Publications *specifically* related to this award that have been accepted since the award began are below:

**McLaughlin, K.A.**, Sheridan, M.A. (2016). Beyond cumulative risk: A dimensional approach to childhood adversity. *Current Directions in Psychological Science*, 25, 239-245.

Sheridan, M.A., **McLaughlin, K.A.** (2016). Neurobiological models of the impact of adversity on education. *Current Opinion in Behavioral Sciences*, 10, 108-113.

Bush, N.R., Lane, R.D., **McLaughlin, K.A.** (2016). Mechanisms underlying the association between early-life adversity and physical health: Charting a course for the future. *Psychosomatic Medicine*, 78, 1114-1119.

**McLaughlin, K.A.**, Bush, N.R., Lane, R.D. (2016). Introduction to the special issue of *Psychosomatic Medicine*: Mechanisms linking early-life adversity to physical health. *Psychosomatic Medicine*, 78, 976-978.

**McLaughlin, K.A.** (2016). Future directions in childhood adversity and youth psychopathology. *Journal of Clinical Child and Adolescent Psychology*, 45, 361-382.

Gold, A., Sheridan, M.A., Peverill, M., Busso, D., Lambert, H.K., Alves, S., Pine, D.S., & **McLaughlin, K.A.** (2016). Childhood abuse and reduced cortical thickness in brain regions involved in emotional processing. *Journal of Child Psychology and Psychiatry*, 57, 1154-1164.

Dennison, M.J., Sheridan, M.A., Busso, D.S., Jenness, J.L., Peverill, M., Rosen, M.L., **McLaughlin, K.A.** (2016). Neurobehavioral markers of resilience to depression amongst adolescent exposed to child abuse. *Journal of Abnormal Psychology*, 125, 1201-1212.

Busso, D.S., **McLaughlin, K.A.**, Brueck, S., Gold, A., Sheridan, M.A. (2017). Child abuse, neural structure, and adolescent psychopathology: A longitudinal study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 56, 321-328.

Lambert, H.K., Sheridan, M.A., Sambrook, K., Rosen, M., Askren, M.K., **McLaughlin, K.A.** (2017). Hippocampal contribution to context encoding across development is disrupted following early-life adversity. *Journal of Neuroscience*, 37, 1925-1934.

Sheridan, M.A., Peverill, M., Finn, A.S., **McLaughlin, K.A.** (2017). Dimensions of childhood adversity have distinct associations with neural systems underlying executive functioning. *Development and Psychopathology*, 29, 1777-1794.

LeWinn, K., Sheridan, M.A., Keyes, K.M., Hamilton, A., & **McLaughlin, K.A.** (2017). The representative developing brain: sampling strategy matters for neuroscience. *Nature Communications*, 8, 874.

**McLaughlin, K.A.**, Sheridan, M.A., & Nelson, C.A (2017). Neglect as a violation of species-expectant experience: Neurodevelopmental consequences. *Biological Psychiatry*, 82, 462-471.

**McLaughlin, K.A.**, Lambert, H.K. (2017). Child trauma exposure and psychopathology: Mechanisms of risk and resilience. *Current Opinion in Psychology*, 14, 29-34.

Nook, E.C., Sasse, S.F., Lambert, H.K.,\* **McLaughlin, K.A.**, & Somerville, L.H. (2018). The non-linear development of emotion differentiation: Granular emotional experience is low in adolescence. *Psychological Science*, 29, 1346-1357.

Rosen, M.L.,\* Sheridan, M.A., Sambrook, K.,\* Miles, Z.,\* Dennison, M.J.,\* Jenness, J.L.,\* Askren, M.K., **McLaughlin, K.A.** (2018). Salience network response to changes in emotional expressions of others is heightened during early adolescence: relevance for social functioning. *Developmental Science*, 21, e12571. doi: 10.1111/desc.12571.

\*\*selected as best paper of the year; *Developmental Science*

Rosen, M.L.\* , Sheridan, M.A., Sambrook, K.\* , Meltzoff, A.N., & **McLaughlin, K.A.** (2018). Socioeconomic disparities in academic achievement: A multi-modal investigation of neural mechanisms in children and adolescents. *Neuroimage*, 173, 298-310.

Sheridan, M.A., **McLaughlin, K.A.**, Winter, W., Fox, N.A., Zeanah, C.H., & Nelson, C.A. (2018). Early deprivation disruption of associative learning: A developmental pathway to depression and social problems in adolescence. *Nature Communications*, 9, 2216, DOI: 10.1038/s41467-018-04381-8

Dennison, M.J., Rosen, M.L., Sambrook, K.A., Jenness, J.L., Sheridan, M.A., **McLaughlin, K.A.** (in press). Differential associations of distinct forms of childhood adversity with neurobehavioral measures of reward processing: Neurodevelopmental pathways to depression. *Child Development*.

Madhyastha, T., Peverill, M., Koh, N., McCabe, C., Flournoy, J., Mills, K., King, K.M., **McLaughlin, K.A.** (in press). Current methods and limitations for longitudinal fMRI analysis across development. *Developmental Cognitive Neuroscience*.

## 5. Conference Presentations

Since data collection completed in May 2018, I have presented the preliminary findings from the study funded by this award at the Flux Society for Developmental Cognitive Neuroscience, as an invited speaker at the 2018 meeting in Berlin:

McLaughlin, K.A. (2018). Dynamic fluctuations in brain activity following exposure to stressful life events: Neural mechanisms linking stress with psychopathology.

## 6. Additional Grants and Awards

I have won the following awards since the grant began in December, 2015:

Distinguished Scientific Award for Early Career Contribution to Psychology, American Psychological Association (APA) – 2016

Gerald R. Klerman Award for Outstanding Clinical Research Achievement, Brain and Behavior Foundation – 2016

Jacobs Foundation Early Career Research Fellowship – 2015

Clarivate Analytics Highly Cited Researcher in each year since the award began (2016, 2017, 2018; given to ~3,000 scientists worldwide across diverse disciplines; 134 in Psychiatry/Psychology)

*Neuropsychopharmacology* Editor's Award for Transformative Original Report (NEATOR) – 2017

I have received additional funding since the grant began in December, 2015:

**R01-MH106482**

National Institute of Mental Health  
“Deprivation and Threat: Dimensions of Early Experience and Neural Development”  
2016-2020, Total Costs: \$3,339,008  
Role: Principal Investigator

**Administrative Supplement to R01-MH103291**

National Institute of Mental Health  
“Child Maltreatment and the Development of Neural Systems Underlying Emotion Regulation”  
2016-2019, Total Costs: \$687,759  
Role: Principal Investigator

**Jacobs Foundation Early Career Research Fellowship**

Mechanisms Linking Childhood Adversity with Psychopathology  
2016-2019, Total Costs: \$150,000  
Role: Principal Investigator

**Raikes Foundation**

“Social and Environmental Influences on Children’s Motivation for Learning: The Role of Childhood Adversity”  
2017-2018, Total Costs: \$16,788  
Role: Principal Investigator

**Research Network on Later-Life Interventions to Reverse Effects of Early Life Adversity**

National Institute on Aging, U24AG047867 sub-contract  
“Improving the Conceptualization and Measurement of Childhood Adversity in Health Research: A Dimensional Approach”  
2017-2018, Total Costs: \$15,000  
Role: Principal Investigator

**R01-MH115004**

National Institute of Mental Health  
“Do dimensions of adversity differentially predict neural development and psychopathology in young children?”  
2018-2023, Total Costs: \$3,745,070  
Role: Co-Investigator