



## **Addressing Mental Health in the Second Decade of Life through Translational Lifecourse Research**

### **Funded Projects**

In this initiative, sponsored by the Harvard Catalyst [Child Health Committee](#), the community was invited to submit applications for pilot grants to foster and enable collaborative research on mental health and the developing brain in the second decade of life across the T1-T4 translational spectrum.

The specific research priority areas represented topics covered as part of the annual Child Health Symposium held on October 6, 2014. Sponsored by Harvard Catalyst's Child Health Committee, the symposium "Mental Health and the Developing Brain in the Second Decade of Life: Research Challenges and Opportunities" brought together leading scientists from across the nation for a dialog with Harvard's child health research community on four topics: (1) Mood Dysregulation, (2) Youth Suicide, (3) Violence, and (4) Concussion and the Developing Brain. For this initiative, the first two focus areas were consolidated into one research priority area: mood dysregulation and its consequences. Applications in response to this RFA related to this research priority area or to the violence research priority area.

All Harvard University-appointed junior and senior faculty members were encouraged to apply for this funding opportunity, and the principal investigator or a co-investigator must have attended the Child Health Symposium held on October 6, 2014.

Six pilot grants were awarded in amounts of up to \$75,000 for each one-year project.

Funding decisions for the Child Mental Health pilot grants were announced in March 2015.

## **Epigenetics, Childhood Adversity, and Sensitive Periods in Adolescent Depression**

Principal Investigator: Erin Dunn, MPH, ScD, Massachusetts General Hospital

Co-Investigators:     Andrea Baccarelli, MD, PhD, Harvard School of Public Health  
                              Takao Hensch, PhD, Boston Children's Hospital  
                              Jordan Smoller, MD, ScD, Massachusetts General Hospital

We propose to test the overarching hypothesis that epigenetic modification is a central biological mechanism explaining how exposure to childhood adversity (e.g., interpersonal violence, socioeconomic deprivation) gets “under the skin” to increase risk for adolescent-onset depression. We hypothesize that the effects of environmentally-induced epigenetic modification are strongest during sensitive periods in development, or windows of time in the lifespan when the developing human brain is particularly vulnerable or sensitive to experience. This hypothesis will be tested in two aims using secondary data from the Avon Longitudinal Study of Parents and Children (n=1,000), a large birth cohort with repeated epigenetic and phenotypic measures. We focus on DNA methylation, one of the major mechanisms of epigenetic regulation. In Aim 1, we will examine the effect of timing of exposure to childhood adversity on epigenetic modification in “sensitive period” relevant genes, or genes that regulate the timing of high plasticity stages during postnatal brain development. In Aim 2, we will investigate, using statistical mediation models, the extent to which epigenetic modification of sensitive period relevant genes mediates or is directly (or indirectly) on the path between timing of adversity and adolescent-onset depressive symptoms. An interdisciplinary team of junior and senior investigators comprising experts across Harvard will accomplish these aims. Findings generated from the proposed research can help identify periods in the lifespan when interventions could be most effective in preventing adolescent-onset depressive symptoms, biological mechanisms by which adversity increases risk for depression, and possible targets to treat depressive disorders.

## **KEeping Youth Safe (KEYS)**

Principal Investigator: Elizabeth Goodman, MD, Massachusetts General Hospital

Co-Investigators: Ari Cohen, MD, Massachusetts General Hospital  
Timothy Wilens, MD, Massachusetts General Hospital

Suicide is the third leading cause of mortality in 10-24 year olds but we have only a rudimentary ability to predict which adolescents will attempt or complete suicide. Because many adolescents use Emergency Departments (EDs) rather than primary care providers for confidential care and to stay “under the radar” of parents, suicide screening in EDs is not only an opportunity, but a responsibility. This pilot study will perform preliminary testing of a developmentally-based adolescent suicide screening algorithm that incorporates primordial through secondary prevention and can be applied universally within EDs while maintaining high efficiency and clinical acceptability. We will evaluate a new 2-step screening algorithm against the state of the art multi-item suicide screener to detect both occult suicidality and future suicidal behavior over 6 months in a cohort of 350 MGH ED 14-19 year old patients seen for general medical/surgical care. Our algorithm incorporates novel single item screeners derived from current clinical practice thereby maximizing goodness of fit and promoting acceptability among ED clinicians. The study will provide critical pilot data for development of a large R01 application for a multi-site study that could transform clinical practice and improve suicide prevention for this vulnerable group.

## **Neural Predictors of Cognitive and Behavioral Correlates of Mood Dysregulation**

Principal Investigator: Dina Hirshfeld-Becker, PhD, Massachusetts General Hospital

Co-Investigators:     John Gabrieli, PhD, Massachusetts Institute of Technology  
                              Brandon Gibb, PhD, SUNY Binghamton  
                              Jamie Micco, PhD, Massachusetts General Hospital  
                              Benjamin Shapero, MA, Massachusetts General Hospital

Despite growing evidence for atypical brain function in depression, it is uncertain whether these functional differences reflect the clinical state of depression or a trait predisposing to depression. We previously studied a group known to be at elevated risk for depression, offspring of parents with depression. Compared to offspring of controls, healthy 8-14-year-old offspring of parents with depression showed increased activation to fearful versus neutral facial expressions in the amygdala and other brain regions, and decreased activation to happy versus neutral expressions in the anterior cingulate cortex and supramarginal gyrus (N=50). The extensive over-activation to negative expressions and under-activation to positive expressions in at-risk children are consistent with behavioral evidence that vulnerability to depression involves a bias to attend to negative information, and may represent a neural marker of risk for depression. However, prospective follow-up studies are needed to elucidate this issue. We therefore propose a follow-up of these youth, now ages 12-18, to examine whether the neuroimaging data collected previously are associated with three specific forms of cognitive vulnerability to depression: biases to attend to negative information, to interpret ambiguous stimuli negatively, and to explain negative events pessimistically; and whether the neural data predict new emergence of depressed mood and other symptoms of emotional dysregulation. This project will generate pilot data for a larger prospective study examining whether early emerging neural differences identified in children at risk for depression contribute to the development of cognitive biases and onset of disorder and will pave the way for targeted preventive interventions.

## **Severe Early Life Neglect, White Matter Microstructural Development, and Internalizing Disorders. Pathways to Long-term Risk and Recovery.**

Principal Investigator: Charles A. Nelson, PhD, Boston Children's Hospital

Co-Investigators:     Johanna Bick, PhD, Boston Children's Hospital  
                              Kate McLaughlin, PhD, University of Washington

Children exposed to early adverse experiences, including severe neglect, are at heightened risk for developing internalizing disorders during childhood and adolescence. Growing evidence suggests that alterations in neural circuitry associated with emotion processing may be associated with increased psychiatric risk. The current study examines whether alterations in white matter growth among children exposed to early life neglect predict risk for depression and anxiety disorders during adolescence. The three objectives of this study are to: 1) examine whether neglected children show reductions in the proliferation and growth rate of white matter across development, 2) test whether altered white matter trajectories are predictive of risk for depression and anxiety disorders during adolescence, and 3) explore whether children assigned to an early intervention show improved white matter trajectories and associated reductions in depression and anxiety symptoms. Adolescence is considered a sensitive point in development during which internalizing disorders are likely to emerge; therefore, the current study specifically examines associations between white matter growth and internalizing symptoms in adolescent youth. Findings have implications for understanding neurobiological mechanisms that link early adversity with risk for youth-onset internalizing symptoms. Results will also inform prevention and intervention efforts to promote healthy development among vulnerable youth.

## **Quantifying Reinforcement Learning Deficits In Adolescent Depression: A Computational Imaging Study**

Principal Investigator: Leah Somerville, PhD, Harvard University Faculty of Arts and Sciences

Co-Investigators: Catherine Glenn, PhD, Harvard University Faculty of Arts and Sciences  
Catherine Insel, Harvard University Faculty of Arts and Sciences  
Matthew Nock, PhD, MPH, Harvard University Faculty of Arts and Sciences

Adolescence is characterized by dramatic increases in psychopathology, suggesting that specific neurodevelopmental processes may confer unique risks during this period. Adolescence is also associated with normative increases in the function of the brain's mesolimbic dopamine circuit, promoting enhanced approach behaviors towards rewards. A second key role for the mesolimbic dopamine system is to guide reinforcement learning, the process of updating value representations based on past rewards. Although prior research has identified functional blunting in reward reactivity in adolescents with depression, the functional consequences of such blunting for reinforcement learning have not been established. This proposal aims to test whether adolescents with depression demonstrate a reduced tendency to learn from positive experiences to predict future rewards and reduced neural signals of reinforcement learning compared to typically developing adolescents. We will use a novel reinforcement learning task that measures the tendency to use feedback to guide future decisions in tandem with neuroimaging. Computational learning parameters will represent individuals' utilization of positive feedback to update future decisions. We will compare depressed and healthy adolescent groups on learning parameters and associated neural recruitment and connectivity in mesolimbic dopamine circuitry. If our hypotheses are supported, they will indicate promise in further pursuing aberrant learning as a neurodevelopmentally grounded, potentially debilitating consequence of the neurobiological aberrations associated with adolescent depression. Blunted reinforcement learning could result in depressed youth having a lessened ability to seek out reward-optimizing experiences in daily life, which could serve as an interventional target to improve the lives of youth with depression.

## **Mechanisms Linking Childhood Maltreatment to Mood Dysregulation in Adolescence**

Principal Investigator: Martin H. Teicher, MD, PhD, McLean Hospital

Co-Investigators: Kyoko Ohashi, PhD, McLean Hospital  
Kerry J. Ressler, MD, PhD, McLean Hospital  
Marisa M. Silveri, PhD, McLean Hospital

Childhood maltreatment is a leading risk factor for mood and anxiety disorders and suicide. We have proposed that risk for psychopathology is related to stress-induced alterations in development of brain regions involved in emotional regulation and have published strongly supportive evidence. However, we know very little about the underlying mechanisms through which exposure to interpersonal violence and early life stress 'gets under the skin' to actually affect brain development and enhance risk for mood disorders. We seek to obtain pilot data that can lead to an initial evaluation of four underlying mechanisms. These include: (1) epigenetic modification of genes regulating stress hormone (cortisol) secretion; (2) epigenetic modification of trophic growth factors including brain derived neurotrophic factor (BDNF); (3) emergence of chronic neuroinflammation; and (4) sleep disturbance leading to persistent sleep debt. Funding from the Harvard Catalyst will enable us to collect and analyze data on these mechanisms in 18-19-year-old subjects currently being recruited for a longitudinal study assessing neuroimaging biomarkers for risk for substance abuse in maltreated individuals. We will calculate the degree to which these mechanisms mediate the association between maltreatment history and severity of mood dysregulation and between maltreatment history and structure and connectivity of brain regions involved in emotional regulation. Delineating mechanisms mediating the effect of abuse is of crucial importance in the development of strategies to protect maltreated adolescents from developing anxiety and depression, or attempting suicide, and may lead to the discovery of novel ways of treating mood disorders in individuals with maltreatment histories.