

child psychiatry outcomes. Epigenetic techniques may allow us as a field to understand the molecular mechanisms that lie between environmental factors and downstream changes in brain and behavior.

**Methods:** We have assembled six leading researchers in the field of epigenetics who have considerable experience translating basic epigenetic concepts for general scientific and clinical audiences.

**Results:** The morning session is an immersive experience focusing on epigenetic mechanisms in relation to prenatal or early life experiences. The three presentations will begin with a description of basic epigenetic mechanisms, extend to seminal work conducted in rodents, and then describe relevant human studies harnessing the power of epigenetic techniques to reveal the impact of distress or neglect. The morning session will conclude with a panel discussion of early life environment and epigenetics. The afternoon session provides examples of epigenetic approaches integrated into specific domains of child psychiatry research, including post mortem research on neurodevelopmental disorders, the gateway hypothesis of substance abuse, and the paternal contribution to epigenetic inheritance. The afternoon session will conclude with a panel discussion that extends to the opportunities and pitfalls of incorporating epigenetic approaches in child psychiatry research.

**Conclusions:** At the end of the Research Institute, participants will understand basic epigenetic mechanisms in the context of child and adolescent developmental outcomes. Participants will have the opportunity to discuss both the types of questions that can be approached with epigenetic techniques as well as the specific, practical choices to be made when conducting epigenetic research.

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#### 2.1 A TALE OF TELOMERES

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**Objectives:** This presentation will begin with a historical perspective on telomeres, factors affecting telomere length dynamics, such as aging, and the link across a range of fields of medicine between adversity and aging. Seminal studies of TL length in adults and children, with descriptions of appropriate caveats and strengths, then will be presented. The results will be presented in relation to models of risk, resilience, biological sensitivity, and the adaptive calibration model.

**Methods:** Data from the following three distinct cohorts will be presented: the Bucharest Early Intervention Project (BEIP), the New Orleans Stress Physiology and Children (NSPAC) study, and the Infant Development Study (IDS). These studies are designed to explore the impact of early adversity, including transgenerational effects, on telomere length; other markers of the stress response systems will be presented as well. Data from all the three cohorts will demonstrate the use of TL across infancy and throughout childhood. Across all three studies, TL and TL decline were associated with a range of different adversities, with significant race and sex moderation.

**Results:** Within the BEIP study, accelerated TL decline from age 6 to 14 years was found in children with a history of institutional care, and at age 12 years, methylation within the serotonin transporter (*5-HTT*) gene was also correlated with the amount of time a child spent in institutional care. Within the NSPAC study, TL, cortisol reactivity, and externalizing were associated with neighborhood level of violence exposure. Lastly, in newborn infants, maternal angiotensin-converting enzyme exposure predicted not only TL at birth but also interacted with race and sex to predict cortisol and respiratory sinus arrhythmia at 4 months of age.

**Conclusions:** Data across the three studies suggest that, beginning at birth, telomere length is reflective of exposure to a range of adversity and stressors, including preconception, environmental, and psychosocial. Models of desynchronous aging and the differential developmental impact on the

stress response systems will be presented. Lastly, the implications of this work for the increasingly common negative health comorbidity found in those with mental illness and future research directions, including efforts to integrate epigenetic and biological markers into treatment studies, will be discussed.

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#### 2.2 EARLY LIFE EXPERIENCES, EPIGENETICS, AND THE DEVELOPING BRAIN

*Frances A. Champagne, PhD, Department of Psychology, Columbia University, 1190 Amsterdam Avenue, 406 Schermerhorn Hall, New York, NY 10027*

**Objectives:** Variation in neurobiological and behavioral outcomes has been associated with both maternal and paternal life experiences, particularly parental exposure to stress, nutritional imbalance, and toxins. We have been exploring the epigenetic mechanisms that account for these parental effects and pathways through which these effects are transmitted across generations.

**Methods:** We have implemented three distinct approaches to study the epigenetic impact of parental experiences that primarily are based on rodent models with translational potential. First, we have examined the impact of maternal stress and toxin exposure during gestation on the placenta and offspring development. Second, we have examined the epigenetic impact of postnatal mother-infant interactions. Third, we have examined how father's experiences directly affect offspring development and how indirect routes of paternal experiences can be achieved through shifts in mother-infant interactions occurring prenatally and postnatally.

**Results:** By use of these approaches, we have determined the following: 1) maternal stress during gestation is associated with gene expression and epigenetic alterations within the placenta that mediate altered neurodevelopment in the fetus; 2) maternal exposure to endocrine-disrupting chemicals during gestation induces sex-specific alterations in brain gene expression, epigenetic variation, and behavior of offspring, with a particular impact on social interactions and learning/memory; 3) the quality of postnatal mother-infant interactions is influenced by both prenatal stress and toxin exposure and can modulate the impact of these exposures; and 4) father's nutritional status experienced before conception of offspring can alter the prenatal maternal environment, the quality of postnatal mother-infant interactions, and neurobehavioral outcomes in offspring.

**Conclusions:** Evidence from both laboratory animal models and human studies suggest that parental experiences can have lasting epigenetic consequences for offspring and that there are unique and interactive routes through which maternal and paternal influences can be achieved.

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#### 2.3 USING EPIGENETICS TO UNDERSTAND HOW DISTRESS DURING PREGNANCY IMPACTS FETAL BEHAVIORAL OUTCOMES

*Catherine Monk, PhD, Psychiatry, Columbia University Medical Center, 622 West 168 Street PH 1450, New York, NY 10032*

**Objectives:** Increased risk of psychopathology is observed in children exposed to maternal prenatal distress, and elevated maternal cortisol and epigenetic regulation of placental glucocorticoid-pathway genes are potential mechanisms. The authors examined maternal distress and salivary cortisol in relation to fetal movement and heart rate ("coupling") and DNA methylation of three glucocorticoid pathway genes—*HSD11B2*, *NR3C1*, and *FKBP5*—in term placentas.

**Methods:** Mood questionnaires and salivary cortisol were collected from 61 women between 24 and 27 gestational weeks, and fetal assessment was conducted at 34–37 weeks. Placental CpG methylation in the three genes was

analyzed using 450K BeadChip Illumina microarray and bisulfite sequencing, correlations between maternal and fetal variables and DNA methylation were tested, and maternal distress effects on fetal behavior via DNA methylation were investigated.

**Results:** Perceived stress (Perceived Stress Scale), but not cortisol, was associated with altered CpG methylation in placentas. In the highest tertile of the Perceived Stress Scale, the BeadChip data revealed modest elevated methylation of *HSD11B2* ( $\Delta$ fractional methylation = 0.034), associated with lower fetal coupling ( $b = -0.51$ ), and modestly elevated methylation of *FKBP5* ( $\Delta$ fractional methylation = 0.030), also with lower fetal coupling ( $b = -0.47$ ). These increases in methylation were validated by bisulfite sequencing where they occurred in a minority of clones.

**Conclusions:** This is the first study to link pregnant women's distress effects on the fetus and epigenetic changes in placental genes. Because increased DNA methylation in *HSD11B2* and *FKBP5* is seen in a minority of bisulfite sequencing clones, these epigenetic changes and functional consequences may affect subpopulations of placental cells. In addition to the specific results, this work is a valuable example of how epigenetics may be integrated into an ongoing clinical research program.

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### 2.4 INTEGRATING EPIGENETIC AND GENETIC RISK IN POSTMORTEM BRAIN RESEARCH

*Shahram Akbarian, MD, Psychiatry, Mount Sinai School of Medicine, Hess Center for Science and Medicine Floor 9 Room 105, 1470 Madison Avenue, New York, NY 10029*

**Objectives:** Less than 1.5 percent of the human genome encodes protein. However, vast portions of the human genome, or approximately 40 percent, are subject to epigenetic regulation, including DNA methylation and hundreds of site- and residue-specific histone modifications, potentially associated with neurological function. Furthermore, there is evidence for widespread epigenomic remodeling of neurons and glia in prefrontal cortex and other brain regions during the course of pre- and postnatal human development.

**Methods:** This presentation will discuss developmental dynamics and disease-associated alterations for multiple layers of epigenetic regulation in human cerebral cortex, including histone methylation and acetylation, histone variant exchange, and chromosomal conformations.

**Results:** Specific examples of how epigenomic studies in neurons and glia mechanistically illuminate the genetic risk architecture of autism and psychosis spectrum disorders, including monogenic neurodevelopmental disease associated with mutations in chromatin regulators, will be provided.

**Conclusions:** Exploration of chromatin structure and function in developing and diseased human brain, and in cultured cells differentiated from pluripotent stem cells, is likely to identify a large number of epigenetic drug targets. In contrast, targeted epigenomic editing of select genomic loci emerges in the animal model as a powerful tool to interfere with cognition and complex behaviors.

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### 2.5 FROM ONE EXPERIENCE TO ANOTHER: A MOLECULAR ANALYSIS FOR SMOKING AND SUBSEQUENT DRUG USE

*Amir Levine, MD, Psychiatry, Columbia University, and New York State Psychiatric Institute, 1051 Riverside Drive, Box 78, New York, NY 10032*

**Objectives:** The Gateway Hypothesis describes a regular developmental sequence in the progression of drug use, in which the use of nicotine/alcohol precedes the use of illicit drugs, and raises an important question that can only be addressed in animal models. Is there a biological basis to explain how the use of a drug predisposes to the subsequent use of another, and if so,

what biological mechanisms underlie this progression of drug use? Here, we use a paradigm of sequential drug exposure to explore how early use drugs, such as nicotine (NIC), and later-use drugs, such as cocaine (COC), alter the transcription levels of select genes in the brain.

**Methods:** Mice were treated with oral NIC for 24 hours or 7 days or acute COC injection. We examined behavioral, electrophysiological, and molecular outcomes of sequential NIC and COC administration in mice. Specifically, we measured subsequent FosB expression in addition to histone acetylation (HA) at the FosB promoter. To explore how HA changes may mimic the effect of NIC on COC, we then examined the effect of histone deacetylase (HDAC) inhibitor suberoylanilide hydroxamic acid (SAHA), activator theophylline on FosB expression, and HA, and we examined the effects of COC in a mouse model of reduced HA. Lastly, we examined these effects in adolescent mice.

**Results:** Pretreatment of 7-day NIC markedly increased sensitization, conditioned place preference, and FosB expression in response to COC, whereas COC pretreatment did not alter FosB expression in response to NIC. We found that NIC primed COC response by enhancing transcriptional activation of the FosB gene through inhibition of HDACs, which caused global striatal HA after COC and enhanced COC-specific changes in long-term potentiation in several brain regions. We also show that SAHA simulated NIC, priming COC response and enhancing FosB expression and LTP depression in the nucleus accumbens. In contrast, theophylline reduced the effects of COC on LTP and FosB expression, which we replicated in a mouse model of reduced HA. Lastly, we found that adolescent mice have increased HA and that NIC caused increased FosB expression and COC response in adulthood.

**Conclusions:** Here, we described the potential neurobiological underpinnings of the Gateway Hypothesis. Our findings suggest that nicotine use may increase the likelihood of abuse and addiction to cocaine and other drugs, such as heroin, that depend on FosB expression.

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### 2.6 AGE-RELATED DNA METHYLATION CHANGES ARE ASSOCIATED WITH ABNORMAL BEHAVIOR IN OFFSPRING

*Jay A. Gingrich, MD, Sackler Institute for Developmental Psychobiology, Columbia University, Columbia University, 1051 Riverside Drive, New York, NY 10032*

**Objectives:** Advanced paternal age (APA) has been shown to be a significant risk factor in the offspring for neurodevelopmental psychiatric disorders, such as schizophrenia and autism spectrum disorders. During aging, *de novo* mutations accumulate in the male germline and are frequently transmitted to the offspring with deleterious effects. In addition, DNA methylation during spermatogenesis is an active process, which is susceptible to errors that can be propagated to subsequent generations. Therefore, we tested the hypothesis that the integrity of germline DNA methylation is compromised during the aging process.

**Methods:** A genome-wide DNA methylation screen comparing sperm from young and old mice revealed a significant loss of methylation in the older mice in regions associated with transcriptional regulation.

**Results:** The offspring of older fathers had reduced exploratory and startle behaviors and exhibited similar brain DNA methylation abnormalities as observed in the paternal sperm. Offspring from old fathers also had transcriptional dysregulation of developmental genes implicated in autism and schizophrenia.

**Conclusions:** Our findings demonstrate that DNA methylation abnormalities arising in the sperm of old fathers are a plausible mechanism to explain some of the risks that APA poses to resulting offspring. I will place this in context of other mechanisms by which paternal epigenetic factors influence the offspring.

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