NIDA Strategic Planning –
Gene x Environment x Development Interactions (GEDI)
Co-Chairs: Naimah Weinberg and Jonathan Pollock
SPB Coordinator: Michele Rankin

Workgroup Webinar
Tuesday, April 28, 2015
3:00 p.m.

Attendees
Co-Chairs: Naimah Weinberg, Jonathan Pollock; **Extramural Workgroup Members:** Hugh Garavan, Kenneth Kendler, Gustavo Turecki, John Rice, Jane Costello, Danielle Dick; **NIDA Staff:** Raul Mandler, John Satterlee, Hal Gordon, Maureen Boyle, Michele Rankin, Emily Einstein; **Public Participants**: Caitlin Dudevoir, Elissa Chesler, Abraham Palmer

Welcome and Overview
Dr. Naimah Weinberg opened the meeting and invited workgroup members to identify themselves and their affiliations.

Presentation of Requested Data from NIDA Staff
Dr. Jonathan Pollock and Dr. Weinberg presented the following information related to workgroup requests from the 4/17 meeting:

1. Workgroup members should have received a list of augmented references for studies presented on April 17, 2015.
2. A review of the NIDA FY14 RCDC Genetics portfolio revealed 150 human studies, 107 mouse studies, 33 rat studies, and studies on a variety of other organisms.
3. A review of the NIDA FY14 RCDC Genetics portfolio (R01s only) showed 27 longitudinal studies, 24 cross-sectional studies (most were molecular, some psychopharmacological), and 13 post-mortem studies.

Discussion
- Studies of invertebrates are hard to get funded through study sections.
- There was only 1 GWAS study in the longitudinal vs. cross-sectional list; Dr. Weinberg will try to identify more and report back to the group.
- The post-mortem studies might be an overestimation; genetics not focus of those studies.
- The ABCD study will contain a wealth of genetic information. The data will need to be assayed before it is analyzed. ABCD is not currently funded for this purpose, but future ancillary funding is likely.
- The history of the NIDA Genetics Consortium shows that funding peaked in 2007 and has been steadily decreasing.

Summary of Major Issues So Far
Dr. Pollock and Dr. Weinberg asked workgroup members to review meeting summaries and notify them if anything needed to be corrected. Thus far, the following recommendations/issues received the highest number of endorsements from workgroup members:

- Large data sets are necessary for conducting GxE research.
- An examination of phenotype and environment is needed.
- Need to prioritize data-sharing on phenotypes.
- Encourage longitudinal study designs and sophisticated causal modeling.
- Promote a multidisciplinary approach to training future GEDI researchers.

Dr. Gustavo Turecki presented a summary of his recommendations that were sent to the co-chairs separately. He indicated a need to prioritize: a) research on epigenetic mechanisms of addiction; b) studies on cell type-specific epigenetic markers in peripheral and CNS tissue; c) translation of epigenetic mechanisms from animal to humans; and d) an examination of small, noncoding RNAs as biomarkers for addiction phenotypes.

Dr. Turecki identified his list of needed resources as: a) generation of epigenetic reference maps from different brain regions; b) biobanks of both human and animal tissue; and c) increased sequencing capacity and bioinformatics tools. He suggested that consistency of research findings between different labs and across animal models and related human phenotypes would be ideal benchmarks, and that increased bioinformatics training was needed. He further recommended leveraging the following technologies: a) CRISPR for targeted modification; b) optogenetics; and c) more efficient vector systems.

Dr. Pollock provided an overview of recommendations received from Dr. Eric Johnson. Dr. Johnson's suggested priority areas included: a) genotyping the many existing samples that lack funding; b) conducting large-scale GWAS for comparison of epigenetics in brain tissue between those addicted and non-using controls; c) identifying biomarkers for addiction; d) requiring sharing of environmental risk factor and phenotype data; e) expanding basic research across the spectrum of genomics to provide insights into HIV + SUDs; f) bringing discovery science tools to real-world treatment settings using large numbers of patients to focus on clinical outcomes; and g) leveraging ABCD biospecimens for linking omics to imaging.

Dr. Johnson recommended increased funding, targeted RFAs, and revising dbGaP requirements to allow for sharing of environmental and phenotype data; training in bioinformatics to integrate data across domains; and leveraging metabolomics and wearable sensors. His list of suggested benchmarks included tracking the: a) number of new samples genotyped under NIDA's existing samples (Smokescreen) project; b) number and success of new awards addressing each targeted area; c) impact of data sharing through citation counts for the shared data sets; d) number of newly shared data sets and resources made available to the research community; and e) number of new, replicated genetic discoveries.

<u>Questions/Comments</u>
Dr. Weinberg indicated that she received other comments from Dr. Bill Iacono and encouraged all workgroup members to forward their feedback in writing. Feedback should not exclude issues already brought forth by other members because it will help to gauge consensus on shared items. She then opened the floor for member comments and questions.

Dr. Jane Costello voiced concern on the paucity of NIDA grants on humans that use GWAS data and suggested the need to concentrate on candidate gene environment studies to build a set of usable candidates for further examination in the context of development and environment. She also stressed the need for longitudinal studies to determine causation.

Dr. Hugh Garavan agreed with most issues raised, including the need for large samples and longitudinal studies, but added that looking at the genetic effects on treatment response is important. He suggested that we might gain more traction in trying to understand who becomes addicted and why by targeting the genetic correlates to the deleterious cognitive effects of drug use. A related point might be to ask what the best biomarkers or outcomes are for measuring these genetic effects. Dr. Garavan also suggested we might want to look at cognitive outcomes or neuroimaging biomarkers versus the traditional diagnostic categories of dependency.

Dr. John Rice reported that a review of dbGaP studies revealed good GWAS data related to smoking, but not a lot related to drug abuse. The only studies on drugs included those with alcohol dependence as the primary phenotype. Dr. Rice believes it is important, from the NIDA perspective, to build up GWAS data using large studies. Dr. Pollock indicated that there are a large number of samples relating to HIV and IDU, and HIV makes up a third of NIDA's research budget. Dr. Weinberg agreed with Dr. Rice's point that there are a lot of data available, but they have not been put together yet, and that's where the need is.

Dr. Rice also brought up the need for methods to do the gene x environment analyses, but said that it's hard to get a straight methods grant. Dr. Weinberg and Dr. Kenneth Kendler agreed that we should look into this. Dr. Garavan also asked if the Big Data Workgroup was looking into methodology.

Dr. Kendler advocated for pursuing the ability to fill the space between the single candidate genes (which have very small proportions of variance) and the candidate genes using new and emerging approaches (and *not* using traditional designs for GWAS data) to provide an important middle strategy. He also suggested addressing specificity/nonspecificity types of questions and stressed the need to be clear about the degree in which biomarkers represent state versus trait and how we want to be careful about screening those biomarkers to ensure that they have high levels of cross-talk stability and are themselves substantially heritable.

Dr. Danielle Dick stated that working with investigators from a diverse set of backgrounds outside genetics might be beneficial. Some of them could make potential contributions to the idea of how genetic risk might unfold in conjunction with the environment and across development. She said that very few genes have risen to the level of genome-wide significance, so it would be helpful to encourage researchers to think about their data in a more organized way to advance genes of interest that could be genotyped in studies where there are more extensive phenotypic, longitudinal, and developmental data. She suggested developing ways to build bridges between large-scale genotyping efforts. Dr. Dick noted that the genetics field has already come together on the idea of sharing and pooling of data. There is less pooling in other fields, so she suggested a shift in policy to help facilitate data sharing.

- Dr. Pollock asked if Dr. Dick was suggesting that biosamples be collected in all studies. Dr. Dick replied that there would be great benefit in going back and collecting data samples from other longitudinal developmental studies. She also pointed out the low cost of gene testing kits.

- Dr. Pollock asked what would be the incentive for researchers to share their data. Dr. Dick said that funding has helped bring together collaborative groups in the field of genetics. Dr. Costello replied that they are doing just that with NIDA funding—trying to get people with longitudinal data sets to add biological measures for interactive use. She also believes people want to share data but lack of funding is an impediment; plus, there are real problems with data integration. It will take a lot of time but she thought it would be worth noting that collecting phenotypical data is more expensive and more difficult to do, so it makes sense to look for studies that have those data collected already.

- Dr. Garavan agreed that investigators are generally interested in sharing data, but noted that some junior investigators are anxious about sharing because their contributions can then get lost. He suggested finding a way to recognize researchers who share as a way to incentivize them.

- Dr. Costello suggested combing through RePorter for work being done outside NIDA because most of these people with SUDs also have other psychiatric and health problems.

- Dr. Elissa Chesler was most interested in looking at the post-exposure environmental effects because most people can use certain substances, while only a fraction becomes addicted. This has been modeled very nicely in some mouse populations using genetically identical mice. It is also convenient to use these populations to look at the stability of biomarkers through very precise points in the process of developing the phenomena of addiction, where we can examine at which behavioral endpoint we see evidence of the biomarker association.

Public Comment Period
No comments were submitted to the group.

Action Items
- Workgroup members will review and reflect on materials received via email (reference list, etc.) and provide the co-chairs with comments or requests for further resources.
- Workgroup members will review meeting summary notes and notify Dr. Rankin of any corrections needed.
- Workgroup members will email suggestions to the co-chairs using the template provided.

Next Meeting
The next WebEx Event is scheduled for Tuesday, May 12, at 3 p.m.