

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

**Workgroup Webinar
Tuesday, May 12, 2015
3:00 p.m.**

Attendees

Co-Chairs: Naimah Weinberg, Jonathan Pollock; **Extramural Workgroup Members:** Kenneth Kendler, John Rice, Danielle Dick, William Iacono, Eric Johnson; **NIDA Staff:** Raul Mandler, John Satterlee, Michele Rankin, Emily Einstein, Joni Rutter; **Public Participants:** Elissa Chesler, Abraham Palmer, David Jentsch

Welcome and Overview

Dr. Jonathan Pollock and Dr. Naimah Weinberg welcomed participants and asked workgroup members to review the April 28 summary slide and to send any corrections and other feedback from that meeting to Michele Rankin. Meeting notes for the April 17 meeting have been approved.

Scientific Challenges and Priorities for GxExD Research

Dr. Pollock reviewed the workgroup's identified research priorities as follows: improved phenotyping, improved methods for gene identification, epigenetic approaches, deeper characterization of environment, and integration of animal and human studies. He explained that the workgroup would discuss these topics today in the context of: a) why they are important, b) how they could be accomplished, c) what resources were needed, and d) the pros and cons of each. He kicked off the conversation by asking the group to focus on the importance of gene x environment studies.

- Dr. William Iacono stated that genetic and environmental processes change over the course of development; their effects are important and likely to affect the phenotypes related to the trajectory of SUDs. These processes are presumably different at different stages, and the phenotypes themselves change over time as well, so understanding the developmental continuity of the phenotype is important. He noted that research is generally based on how people look when they are grown up, but figuring out how they got that way involves gene-environment interaction. The challenges to studying GxE mechanistically have been stated in previous meetings, but Dr. Iacono added that past genetic research has not produced the expected results. GxE studies have not been replicable, and there have been no studies on the *developmental effects* of GxE.
- Dr. Eric Johnson agreed that GxExD is important to the development of SUD and addiction, and that the challenge is determining how to address or detect relatively small genetic events and then looking at interactions with changing environment and time or development. Trying to study all three variables at once will be extraordinarily difficult in one study, so Dr. Johnson suggested focusing on gene discovery as a more realistic

first step. He said that some data on environment and development have been produced from a few longitudinal studies. To learn about the mechanisms involved with GxE, we need to have very large samples, or we need to have variants that we know are associated with the outcomes and then look at GxE before progressing to GxExD.

- Dr. John Rice agreed that we can't get a big enough sample for all variables and that it is more realistic to approach GxExD in stages vs. trying to accomplish it in one study.
- Dr. Kenneth Kendler also endorsed the previous comments. He voiced concern, however, over use of the term "interactions." We want to develop models that show joint effects of genes and environment, but sometimes there will be interactions and sometimes there won't. Dr. Kendler also asked if it was more prudent to develop shallow phenotyping to maximize the number of people studied per budget, rather than conduct web-based assessments. He suggested there may be a way to develop an optimal compromise between studying and building in questions on development and environment, adding that polygenetic methods will provide a middle range that has some predictive power.
- Dr. Danielle Dick questioned the ordering of the approach, but agreed with Dr. Kendler's point that the issue is much broader than simply GxE. She explained that it involves how genes and environment are acting *across* development—the processes might be additive or correlational. If we are trying to understand pathways of risk, we should be looking at all of these things.

Dr. Weinberg announced that while the 5 priority challenges were identified by the workgroup, other cross-topic issues were brought up in the feedback received, and these would be addressed during today's discussion. She said the first priority surrounded the need to improve phenotyping, with some differences in the approaches involving state versus trait; integrating imaging and genetic data; challenges of developmental imaging data; leveraging the ABCD data; and addressing the heterogeneity of samples and of substance users.

- Dr. Iacono suggested that biomarkers in terms of endophenotypes would be more challenging than metabolites of drug use. Phenotyping that is not related to metabolism of substances may not be helpful to gene identification. Dr. Iacono explained that they conducted GWAS on 17 phenotypes from 5,000 people, but it did very little to help identify genes. He also is skeptical about imaging data helping with gene variance due to the need for large-enough samples. He added that the ABCD study will have in-depth phenotyping and imaging data and that NIDA should plan to take advantage of the study. The utility of biomarkers is important for getting us closer to a gene product, and they will be more tractable than surveys, but there is not a lot of evidence to show success.
- Dr. Pollock and Dr. Iacono agreed with the idea of identifying a gene and learning its function before applying discoveries from larger data sets. The idea is to test hypotheses with smaller samples to flesh out the relevance of environment and development.

Dr. Weinberg stated that phenotyping was identified by several members of the workgroup as an important challenge to consider for GxExD research. She asked for group input to explain why it is important to improve phenotyping.

- Dr. Iacono said improved phenotyping will get us closer to identifying genes.

- Dr. Johnson and Dr. Kendler pointed out that it is a matter of balancing the quality of study design and quality of phenotype, using larger samples. The phenotype for major depression is more heterogeneous than for schizophrenia. Although unproven, the use of biomarkers dealing with drug metabolism may be potentially useful as a phenotype.
- Dr. Kendler stressed that you cannot separate phenotyping from sample selection. He also mentioned cotinine markers as a potentially important data set.
- Dr. John Rice acknowledged that it will be frustrating to try and harmonize phenotyping across studies, so we need to develop a core set of variables to be applied to all studies due to the heterogeneity of substance use and problem patterns. Dr. Dick added that externalizing and internalizing subtypes are important variables to consider. Dr. Rutter suggested following the Phoenix model for addressing standardization.
- Dr. Raul Mandler agreed with Dr. Rice but noted the importance of leveraging electronic information on patients. This data will be somewhat uniform and can be used to construct questionnaires for comparisons. He stressed that we need to know basic information that can be translated into sub-phenotypes before moving further with sophisticated technology.
- Dr. Weinberg asked how this could be accomplished and if we had a contract that measures metabolomics. Dr. Pollock said that metabolites for substances are studied by the Intramural branch.
- Dr. Joni Rutter and Dr. Weinberg asked for input about other potentially useful biomarkers and suggested developing FOAs and other resources.

Dr. Pollock suggested there might be a way to look at genetic modifiers by environment. He asked the workgroup to discuss why that would be important and what resources were available to help us better understand the genetic architecture.

- Dr. Johnson stated that he agreed with previously identified reasons as to why it is important. He reiterated the need to start with G in order to do GxE, so we will need to identify some of those variances. Whole-genome sequencing to date has been found with GWAS outside the addiction area, but those associations showed small effects so he wouldn't recommend sequencing when looking at rare variances because it wouldn't qualify as gene discovery. Dr. Johnson was less interested in missing heritability but more concerned with identifying variances that will give us clues about the pathways affected by substance abuse.
- In response to a question by Dr. Rutter, Dr. Johnson said there are two ways that genetic epidemiologists can look at variances: those identified with statistical associations to see which reveal putative expression or methylation QTLs to provide some sense of what the biological function might be; or to prioritize variance of discovery that has evidence of a putative functional consequence. Integration can be very important to both identifying initial variant associations, and for understanding the potential consequences of those variances. He added the need to conduct animal studies of those variants and regions.
- Dr. Rice agreed with the idea of determining variances. He noted that there are a lot of databases maturing, but he views looking at data as the second step (following gene identification). He and Dr. Iacono discussed the value and associated costs of conducting whole-gene sequencing for archival data.

- Dr. Kendler voiced concern over access to subjects for appropriate data collection. Researchers will need to study tens of thousands of subjects with serious forms of addiction, ethnic diversity, and different patterns of comorbidity. He recommended that NIDA needs to think about how they want to organize an effort with sample sizes as large as we need them to be. If the goal is to collect these signals toward gene identification, then GWAS will be most efficient way to discover the variants, using a wide variety of statistical approaches to examine existing data. The next step would be to try and relate to environmental and developmental characteristics and tracking them along the etiological pathway.

Public Comments

- Dr. David Jentsch stated that there is emerging evidence coming from genetic reference populations about real genetic correlates of dimensions of substance use and related behaviors. He said that focusing on known genetic correlates would be the best approach for improving phenotyping, especially developmentally regulated genetic correlates of related behaviors.
- Dr. Rutter shared comments received from Dr. Abraham Palmer, suggesting a major priority should be assigning a group of people to follow up on genes that have been found. This has been a major mission in other initiatives, such as Psychiatric Genomics Consortium (PGC). Dr. Palmer indicated that polygenetic methods can be a very powerful tool for integrating GWAS and phenotypes for addiction, which would be helpful in identifying the right animal traits to study. He added that animal studies lend themselves to good biological followup.
- Dr. Elissa Chesler agreed with the idea of using animal models, sharing her experience with integrating experimentally derived data sets in model organisms with associations from human genetic studies. She said that they are using these large data sets to try and map gene associations and identify animal models that are most relevant to specific items that are being assessed in clinical populations. As far as the use of reference populations, including a lot of the mouse populations and other species, Dr. Chesler stressed the relevance to gene-environment interactions and development because genetically identical populations can be followed under many different, independently administered tests over time. She said that mouse models can be powerful platforms for looking at GEDI interactions, and they are more affordable than studying a large human population.

Next Meeting

The next WebEx Event is scheduled for Tuesday, May 26, at 3 p.m.