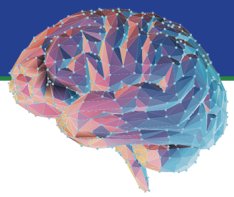


ABCD Insights & Innovations Meeting (AIIM)
Natcher Auditorium, NIH Campus, Bethesda, Maryland
March 4–5, 2024

Introduction & Overview

The inaugural ABCD Insights and Innovations Meeting (AIIM) convened neuroscientists and other researchers from around the world to discuss research using data from the National Institutes of Health (NIH)-supported Adolescent Brain Cognitive Development℠ Study (ABCD Study®)

Launched in 2016, the ABCD Study is a 10-year longitudinal research effort collecting data from approximately 12,000 youth and one caregiver of each participating youth at 21 research sites across the country to better understand the dramatic brain development that occurs in adolescence. Working with participants ages 9–10 at baseline, ABCD Study researchers annually collect data on neurocognition; physical and mental health; substance use (e.g., nicotine, alcohol, cannabis); youth activities and experiences (e.g., screen time, sports, arts); family, neighborhood, and environmental factors; and many others. Researchers also perform brain imaging biennially. These data and brain images have provided and will continue to provide researchers with robust information so they can explore the environmental, social, genetic, and biological influences on brain and cognitive development, behavior, and health.

AIIM included poster presentations, virtual posters, networking and mentoring opportunities, and lunchtime discussion groups. The meeting also featured research presentations, flash talks, and panel discussions, which are summarized below.

Day 1 Welcome & Opening Remarks

The lead meeting planner—LCDR Traci M. Murray, Ph.D., M.P.H., RN, the ABCD Study's Scientific Advisor for Justice, Equity, Diversity, and Inclusion—opened the inaugural AIIM, welcomed participants, and shared logistical and housekeeping information. Dr. Murray briefly introduced the speakers giving opening remarks: National Institute on Drug Abuse (NIDA) Director Nora D. Volkow, M.D., National Institute on Alcohol Abuse and Alcoholism (NIAAA) Director George F. Koob, Ph.D., and National Institute of Mental Health (NIMH) Deputy Director Shelli Avenevoli, Ph.D.

Dr. Volkow stated that the ABCD Study represented one of NIH's most spectacular projects. She praised the investigators and NIH staff members associated with the ABCD Study and specifically acknowledged ABCD Study Director Gayathri J. Dowling, Ph.D., Dr. Koob, NIDA Division of Extramural Research Director Susan Weiss, Ph.D., and NIMH Director Joshua A. Gordon, M.D., Ph.D. Dr. Volkow reminded participants of the challenges associated with the launch and the initial funding of an open-access integrated data science study and other challenges associated with recruiting almost 12,000 youth participants. Projects such as the ABCD Study now occupy the forefront of science, and between the launch of the project and the present day, researchers and NIH staff members have learned how to manage a large, complex open-access longitudinal database that is widely used by scientific investigators.

* Questions and answers are paraphrased.

The ABCD Study is helping investigators address important areas of NIDA's research mission, such as the effects of cannabis exposure on adolescent brain development and cognition. The ABCD Study has also advanced our ability to assess risk for substance use disorder (SUD) and mental illness, to develop models and diagnostics for extracting information from imaging, to identify social determinants of health (SDoH) that adversely affect the developing human brain, and to explore associated disparities. These discoveries will help to improve interventions, prevention efforts, and policy. The ABCD Study's open-access data set has been widely used beyond the ABCD consortium such that 90% of AIIM presenters are not affiliated with the ABCD Study.

Dr. Koob welcomed participants, reiterated the success of the program, and thanked investigators and NIH staff members, particularly Dr. Dowling and Dr. Weiss. The ABCD Study is an extraordinary resource and holds great potential for future studies. Dr. Koob stated that the conversation around alcohol use has changed recently. Underage drinking has steadily declined over the past 20 years. This period of time has also seen the age group with the highest rate of binge drinking go from 18-to-25-year-olds to 26-to-34-year-olds, and the ABCD Study cohort will soon age into the 18-to-25-year-old group. However, women now binge drink more than men, particularly college-age women but also women in most other age groups. Dr. Koob encouraged AIIM participants to consider this fact as they pursue studies with ABCD data. Dr. Koob acknowledged AIIM presenter John A. Matochik, Ph.D., who is a Program Officer in NIAAA's Division of Neuroscience and Behavior, and encouraged participants to contact him with any ABCD-related questions pertaining to alcohol. Finally, Dr. Koob highlighted the *Alcohol Facts and Statistics* living document on NIAAA's website.

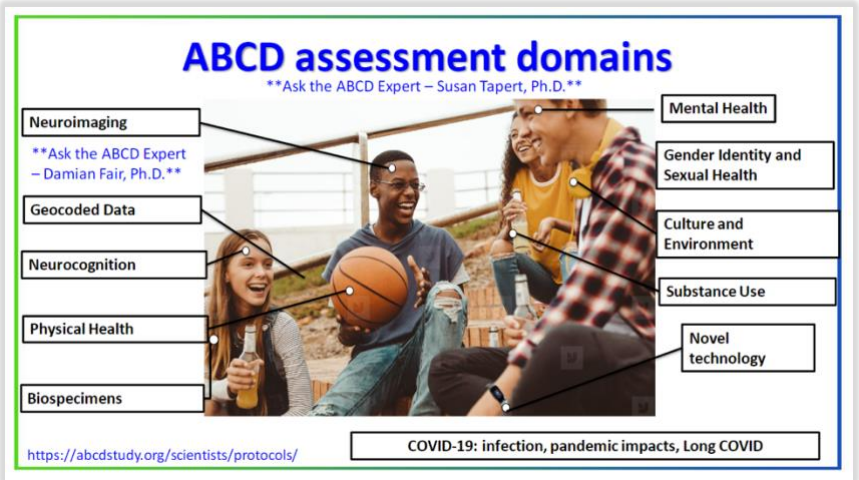
Dr. Avenevoli noted that NIMH's mission is to transform the understanding and treatment of mental disorders and that the institute does so in part by supporting the ABCD Study, a well-managed resource. With the high prevalence of mental health issues among youths and associated calls from the U.S. Surgeon General and others to address them, the ABCD Study is particularly timely and helps to address mental health issues, including SUDs, which often emerge in adolescence. The ABCD Study will help us to determine when, where, and how to best intervene to prevent or stop the course of mental illness. Every ABCD data release expands the understanding of mental illness. Dr. Avenevoli thanked ABCD staff members, investigators, trainees, and adolescent participants and their families. NIMH funds many studies that use ABCD Study data through multiple grant mechanisms spanning all career stages, from research project grants to career development awards. NIMH-supported studies using ABCD Study data address the youth mental health crisis; the increasing rates of youth suicide, suicidal ideation, suicide attempts, and related injury during developmental periods such as childhood and adolescence; the effect of childhood psychotic-like experiences on later-life mental illness; the negative impact of the COVID-19 pandemic on mental health in youths; and the uneven mental health effects of the pandemic on different racial and ethnic groups.

* Questions and answers are paraphrased.

Understanding the ABCD Study

Gayathri Dowling, Ph.D., Director, ABCD Study, NIDA

Dr. Dowling described the ABCD Study as a longitudinal study of approximately 12,000 children from ages 9–10 to early adulthood that assesses factors that influence individual brain development trajectories and functional outcomes. NIH initiated the ABCD Study for several reasons. (1) Adolescence is a time of extraordinary physical, emotional, and intellectual growth. (2) Investigators needed such a study to answer certain research questions that required data from a large longitudinal cohort who were followed prior to the initiation of substance use and the onset of mental illness and then through the period of highest risk. (3) The landscape of substance use—particularly cannabis use, vaping, and associated policies—is currently in flux. (4) Technological advances enabled a multisite neuroimaging study and data sharing with the scientific community. (5) Broad interest prompted support from an initial three and now 10 NIH institutes, centers, and offices (ICOs), as well as the Centers for Disease Control and Prevention. The ABCD Study consortium recruited 11,878 9- and 10-year-olds between 2016 and 2018, largely through school-based recruiting initiatives, to create a cohort that reflects the demographics of the U.S., and partnered with twin registry sites to recruit more than 2,000 twins into the cohort to enable detailed study of gene–environment interactions.

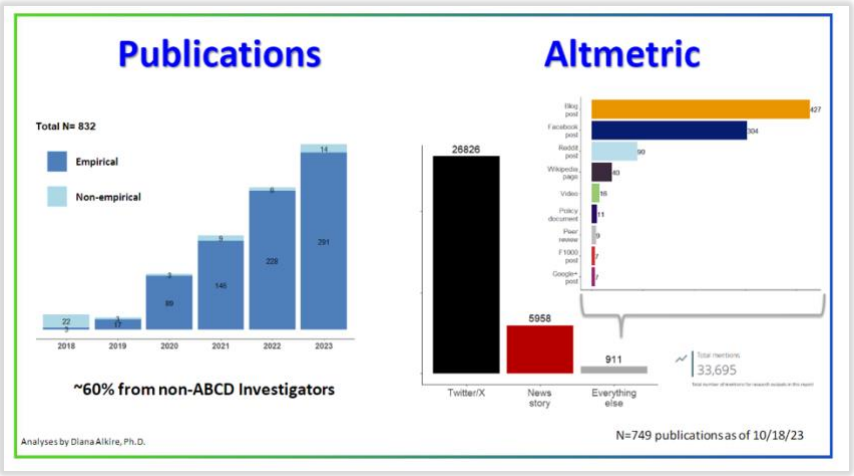


Dr. Dowling briefly reviewed ABCD's assessment domains, which include neuroimaging; physical health; mental health; gender identity and sexual health; substance use; culture and environment; novel technology; neurocognition; biospecimens; geocoded data; as well as COVID-19 infection, pandemic impacts, and long COVID. Dr. Dowling directed meeting participants to Susan Tapert, Ph.D., of the University of California, San Diego (UCSD) and Damien Fair, Ph.D., of the University of Minnesota for more information about ABCD protocols during the Ask the Expert lunch session on Day 2 of the meeting. Dr. Dowling also shared details about the ABCD Linked External Data (LED), which includes residential history–derived geocoded information on urbanicity, state policies, air pollution, residential information, and other characteristics relevant to SDoH. Dr. Dowling referred the audience to Carlos Cardenas-Iniguez, Ph.D., of the University of Southern California for more information on LED during the Ask the Expert session. The 10-year ABCD timeline involves a full data collection protocol every other year, including imaging, and a shorter protocol without imaging every year. The 8-year follow-up will begin in the fall of 2024.

* Questions and answers are paraphrased.

The ABCD Study promises to help answer NIH's initial ABCD research questions, to inform additional research questions arising since the study launched, to pool with other data sets, and to inform development of new methodologies and tools. NIH has made the data available through the NIMH Data Archive (NDA). Dr. Dowling directed meeting participants to Janosch Linkersdörfer, Ph.D., of UCSD and Wesley Thompson, Ph.D., of the Laureate Institute for Brain Research for more information on using the data during the Ask the Expert session. Dr. Dowling also recommended the Day-2 presentation by ABCD Study Associate Director Elizabeth Hoffman, Ph.D., on the ABCD data resource. NIH also recently launched the NIH Brain Development Cohorts (NBDC) Biospecimen Access Program, which makes available specimens collected from participants. Kimberly LeBlanc, Ph.D., Scientific Program Manager of the ABCD Study, provided more information on Day 2 of AIIM.

To date, 15 ICOs—far more than were involved in the launch of ABCD—have funded 208 grants to study ABCD data. Investigators use ABCD data to inform a wide range of studies, most notably magnetic resonance imaging (MRI) and mental health studies, but most analyze ABCD data in cross-category studies. For instance, investigators can merge imaging data, neurocognitive data, and mental health information to answer questions of interest. Over 900 publications have included ABCD data, approximately 60% of which have been authored by scientists not affiliated with ABCD. Several measures of data impact—including the Relative Citation Ratio (RCR) and the Altmetric Attention Score—suggest that the ABCD Study has had great success and reach among the scientific community, the general public, and policymakers.



ABCD staff members have begun to disseminate findings to ABCD families, health care providers, educators, and others who can use the data and put them into practice. A few webinars and infographics on sleep and screentime represent early examples of these efforts, and a forthcoming infographic on COVID-19 will expand these products. ABCD data are also beginning to appear in policy papers, suggesting that the ABCD Study will realize real-world benefits for U.S. youths.

Dr. Dowling concluded by thanking ABCD's Federal partners, research sites, investigators, research assistants, staff, participants, and their families.

* Questions and answers are paraphrased.

Scientific Data Session #1: Cognition/Brain Development (Moderator: Hugh Garavan, Ph.D., University of Vermont)

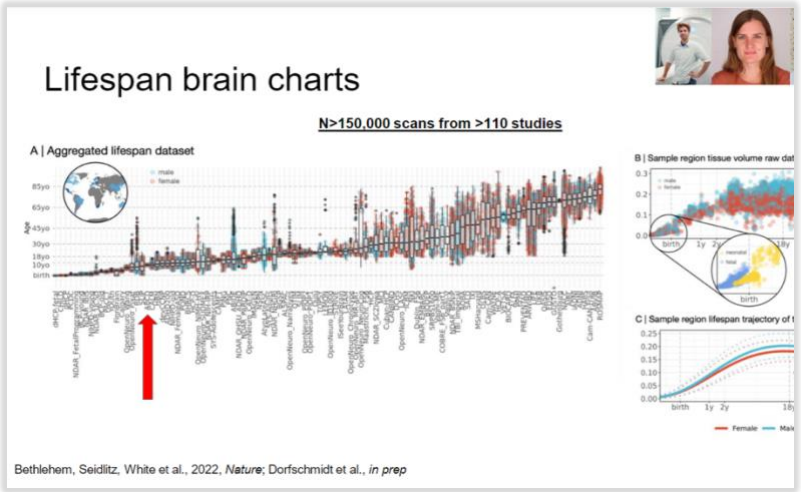
Dr. Garavan introduced the three complementary themes of Scientific Data Session #1: how best to chart brain development (longitudinal trajectories versus cross-sectional), what influences development (e.g., how sleep influences development), and how best to capture individual differences (e.g., in the human connectome).

Obstacles for Individualized Charting of Brain Development

Jakob Seidlitz, Ph.D., Children's Hospital of Philadelphia and the University of Pennsylvania

Adolescence is a critical period from both a neurobiological perspective and a mental health perspective. For instance, the average age of onset for many neuropsychiatric disorders is 10–20 years. Aberrations in neurodevelopmental processes are associated with many of these disorders, and some of these aberrations start and end prior to ABCD neuroimaging at age 9 or 10. Dr. Seidlitz proposed a visual metaphor of motion parallax, i.e., objects that are closer appear to be moving faster than objects farther away, to suggest a parallax of brain development. In this analogy, cross-sectional data points, even those among a set of longitudinal data points, constantly reflect the neurodevelopment of an individual up to a given time point but also inform outcome predictions. How do we reconcile this parallax of brain development with brain imaging across the life course? Charting constantly moving brain development requires big data—both across a large number of individuals and within single individuals at various time points across the life course. Big data enables us to chart typical brain development trajectories, as well as aberrant trajectories, and to understand imaging-derived phenotypes in terms of various outcome measures.

Dr. Seidlitz's research aggregates massive data sets across the lifespan to chart brain development at the population level. The study began with whole-tissue volumes and anatomical regions to create brain development charts and to derive interpretable percentile scores, such as the ones pediatricians use for height and weight, for different brain imaging features that are readily comparable across studies. By mapping milestones that occur at the population level, researchers can start to unpack the longitudinal data on how these trajectories may differ.

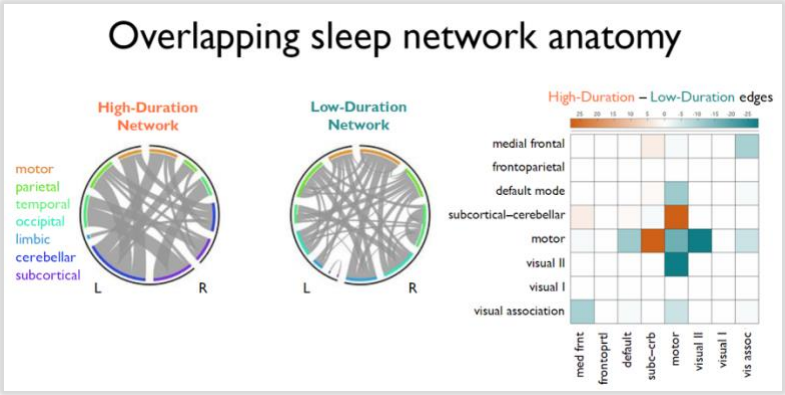


Models derived from longitudinal data, however, show differences in cross-sectional derived features. It is important to remember that cross-sectional charts are a trajectory of distributions not a distribution of trajectories. This is evident when we compare how individuals change in their percentile scores but not necessarily in their raw phenotypic values. We can characterize

* Questions and answers are paraphrased.

this with “thrive lines,” approximated from cross-sectional models that reflect how we expect an individual to change over time and across centiles.

Other researchers have demonstrated that phenotypes derived from big data studies across individuals can inform smaller studies. Several posters presented at this meeting demonstrate this type of work (e.g., Kang et al., Poster 20, Day 2; Murtha et al., Poster 23, Day 1), leveraging study design features and analytic designs to create more reproducible and robust inferences from the data.



Connectomes Reflect Sleep Habits

Monica Rosenberg, Ph.D., University of Chicago

A large body of research establishes that individual functional connectivity—estimated from resting state and task-based functional MRI (fMRI)—predicts individual cognitive and attentional abilities. These unique connectivity patterns reflect individuals’ environments (e.g., neighborhood-level air pollution) and experiences, not just their traits and behaviors. Sleep, which is dictated by environment and biology, is critical in childhood and adolescence (and across the lifespan). Insufficient sleep affects cognitive function, physical and emotional health, and school performance, but at least 30% of adolescents in Europe, North America, and Asia experience poor sleep.

Sleep relates to functional brain architecture. Sleep deprivation decreases within-network integration and between-network segregation. Functional connectivity patterns correlate with adult sleep habits. ABCD data analyses have shown that functional connections mediate effects of insufficient sleep on youth cognition. The Rosenberg lab studies how individual connectivity patterns predict individual cognitive and attentive function.

One study tested how individual connectivity patterns may predict individual sleep duration among youths. ABCD 2-year follow-up data on Fitbit-estimated sleep patterns among 11- and 12-year-olds (patterns that only moderately correlate with caregiver and youth self-reports) show that youths sleep on average 7 hours and 25 minutes a night, far less than recommendations. Machine learning models using *n*-back task data (which reflect individual functional connectivity while performing a working memory task) can significantly predict sleep duration. However, machine learning models using resting-state data predict sleep duration significantly better than *n*-back task data models. Outstanding questions include: Do these models predict sleep duration or Fitbit-measured minutes slept? Do these models predict sleep in people in general or only among the 11- and 12-year-olds in the ABCD Study with low head motion?

Dr. Rosenberg’s lab then found that the youth-defined resting-state model developed with an objective measure (i.e., FitBit) was also able to predict adult sleep duration based on the

* Questions and answers are paraphrased.

Human Connectome Project dataset, which is based on self-report sleep duration. The researchers also found significant overlap of the networks that predict sleep in both datasets. Finally, models trained to predict sleep also explain significant amounts of variance in cognitive performance on the *n*-bask task, suggesting another potential link between them.

Dr. Rosenberg concluded that (1) functional connectivity patterns predict objective and subjective measures of typical sleep duration; (2) common functional networks observed at rest predict sleep duration in adolescents and young adults; (3) models trained to predict sleep duration capture significant variance in cognitive performance; and (4) researchers building and interpreting connectome-based predictive models should consider how sleep affects brain networks and behavior. Future work could consider causal associations between connectome organization and sleep, predictors of different features of sleep (e.g., sleep quality), and the influence of state-like factors on trait-level brain-based predictions.

Dissociable Representational Dimensions Reveal Scales of Individual Differences in the Functional Connectome

Erica Busch, Yale University

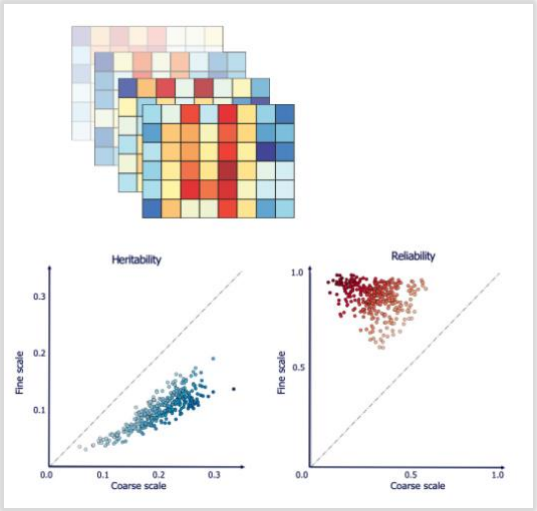
Researchers commonly think about the brain as sets of regions or networks and often average individual signals within each region to yield aggregate time series. This process reduces dimensionality, removes noise, and enables comparison of coarse functional structure across individuals—which is useful for ABCD and other large sets of brain imaging data. However, underlying this coarse structure are individual signals that researchers generally collapse. Within MRI data, each individual voxel has its own response profile and connectivity profile. Voxels fluctuate over time and traverse a high-dimensional space, which can afford a more complex, nuanced understanding.

To link brain imaging data to behavior or cognition, researchers commonly extract an aggregate signal from whole-brain fMRI data for different regions of the brain to yield a "coarse connectome," which research shows is heritable, individual-specific, and predictive of cognition. However, fine-scale connectomes, which correlate the voxel patterns for a given region and the signal from each other region in the brain, are also individual-specific and predictive of intelligence. Prior work has not considered the fine-scale connectome in children. Ms. Busch's research asks how heritable and individual-specific information is represented in the developing functional connectome.

She addressed this question with ABCD data from the twin sites, exploring resting-state fMRI data, coarse (parcel-wise) connectivity, and fine (vertex-wise) connectivity. Researchers conducted a "hyper-alignment" process, i.e., a set of transformations that maximally aligns the functional connectomes across participants, such that when there are mismatches, there is increased confidence that they are due to reliable functional differences. Investigators performed connectivity hyper-alignment on fine connectivity data from 200 brains of unrelated participants to yield a normative model of the brain. Next, researchers aligned fine-scale connectome data from over 900 other subjects to the normative model and recomputed those connectomes after hyper-alignment. This process highlighted shared patterns of functional

connectivity across subjects and emphasized how the subjects reliably differed from one another.

Researchers compared the coarse and fine connectomes with three metrics: multidimensional heritability, the reliability of individual differences in functional connectivity, and the prediction of individual differences in general cognition and learning/memory. Results show greater heritability in the coarse-scale connectome and lower heritability in the fine-scale connectome; but greater reliability in the fine-scale connectome than the coarse-scale connectome. Investigators then compared how predictive the coarse- or fine-scale connectomes were for general cognition, which is known to be more heritable, and learning and memory, which is less heritable. There was no difference in the predictivity between the coarse and fine-scale connectivity for general cognition; however, for learning and memory, the fine-scale connectomes predict scores significantly greater than at the coarse scale.



Ms. Busch concluded that (1) high-dimensional functional alignment improved reliability and the behavioral relevance of functional connectivity; (2) heritable information is represented more strongly in the coarse structure, whereas individual-specific information is represented more strongly in the fine structure; and (3) multiple representations of brain activity can yield insight into neural correlates of behavior.

Q&A*

Q (in-person participant): Does Dr. Rosenberg's prediction model have clinical applications?

> A (Dr. Rosenberg): The model cannot serve as a diagnostic for sleep dysfunction at this time. Researchers have not considered how Fitbit data, self-reported sleep duration data, and cognitive function data could inform clinical decisions at this stage.

Q (in-person participant): Could the greater predictability associated with the resting data reflect slow-wave activity showing insufficient consolidation during poor sleep?

> A (Dr. Rosenberg): The researchers did not consider the relative predictive power in different quartiles of the sample. The predictions were statistically significant but not perfect. Whether the predictive power would scale in those who sleep the most is an open question. Why resting-state data are most predictive is also an interesting question. Generally, task data are more predictive.

* Questions and answers are paraphrased.

Q (Dr. Volkow): How do we take the factors that affect sleep patterns, such as noisy environments and disruptive household behaviors, into account?

A (Dr. Rosenberg): Differences in sleep stem from stress, physical and social environments, and other factors. The fact that the ABCD study has different data types represents a strength, and researchers will be able to build these experiences into future models.

Q (virtual participant): Does sleep predictability from resting-state data differ for different ages?

A (Dr. Rosenberg): We examined only the 2-year follow-up data, but there is little difference in predictive power between adult resting-state data and ABCD data.

Q (virtual participant): Could resting-state data reflect an individual's state just prior to sleep, which could influence the amount sleep?

A (Dr. Rosenberg): We have not considered that, but it is a worthwhile question.

Q (Dr. Garavan): Can you provide guidance on cross-sectional analysis of ABCD data (e.g., cortical thickness)?

A (Dr. Seidlitz): Longitudinal data are needed to gauge trajectory and peaking of cortical thickness and other phenotypes. Other variables, such as sleep and codependence, can play a role. We try to enable use of brain imaging features to pinpoint an individual either longitudinally or cross-sectionally in relation to the population. We also want to rule out the contribution of neuroanatomical differences in fMRI analyses.

Q (in-person participant): Are ABCD data compatible with FreeSurfer data?

A (Dr. Seidlitz): We primarily use FreeSurfer data from ABCD, along with data our team generated. However, researchers should keep up with state-of-the-art technology in phenotyping and harmonize data between different scanners and sites.

Q (Dr. Garavan): Why are fine-scale data more reliable?

A (Ms. Busch): Fine-scale data are more reliable both before and after hyper-alignment. The increased reliability may stem from the nature of the metric, which measures how different people are from others within a sample. People are reliably more similar to themselves than anyone else.

* Questions and answers are paraphrased.

Q (virtual participant): How can ABCD researchers using Ms. Busch's methodologies get the best and most accurate results?

A (Ms. Busch): Researchers need to consider carefully what they want to study. Fewer computational resources are needed for coarse-scale functional connectivity analyses, but fine-scale connectomes can highlight specific features more clearly.

Q (in-person participant): How do you reconcile brain development charts, which would be useful across the lifespan, with ABCD data, which start with participants at ages 9–10?

A (Dr. Seidlitz): Researchers must carefully consider their covariate structure in their analyses.

Q (Dr. Garavan): Can you provide guidance on the poor correlation among Fitbit data, youth self-reports, and caregiver reports?

A (Dr. Rosenberg): Poor correlations suggest either that the subjective measures represent noisy estimates or that the three measures index different aspects of sleep. Researchers should collect multiple types of data on sleep duration to get a more complete picture.

Q (Dr. Volkow): What are the reproducibility and reliability of fine- and course-scale data from imaging taken from the same individuals on different days and in different states? Also , do you have more information on the degree of predictability anticipated for an ongoing longitudinal study?

A (Ms. Busch): Other researchers, perhaps using other data sets, studied the reliability of fine-scale connectivity with task data over time. These researchers found fine-scale connectivity to be more reliable than coarse-scale metrics. However, these investigations have studied neither children nor resting-state data.

Q (in-person participant): Can you speak to the apparent trade-off between heritability and reliability and what drives the greater reliability and lower heritability of fine-scale connectomes?

A (Ms. Busch): There is a trade-off between the coarse and fine scales. Individual experience most likely drives the greater reliability of the fine-scale data.

Lunch Session: Program Officer Panel (Moderator: Vani Pariyadath, Ph.D., NIDA, Behavioral and Cognitive Neuroscience Branch)
John Matochik, Ph.D., NIAAA, Division of Neuroscience and Behavior
Lindsay Pool, Ph.D., National Heart, Lung, and Blood Institute (NHLBI), Division of Cardiovascular Sciences
Jenni Pacheco, Ph.D., NIMH, Development Mechanisms and Trajectories of Psychopathology Branch

* Questions and answers are paraphrased.

Sundania Wonnum, Ph.D., National Institute on Minority Health and Health Disparities (NIMHD), Division of Clinical and Health Services Research

Scientific Data Session #2: Mental Health (Moderator: Ashley Smith, Ph.D., NIMH Division of Translational Research)

Dr. Smith introduced the session on using ABCD data to provide insight into mental health across developmental stages. She noted that the speakers span disciplines, methodologies, and career stages.

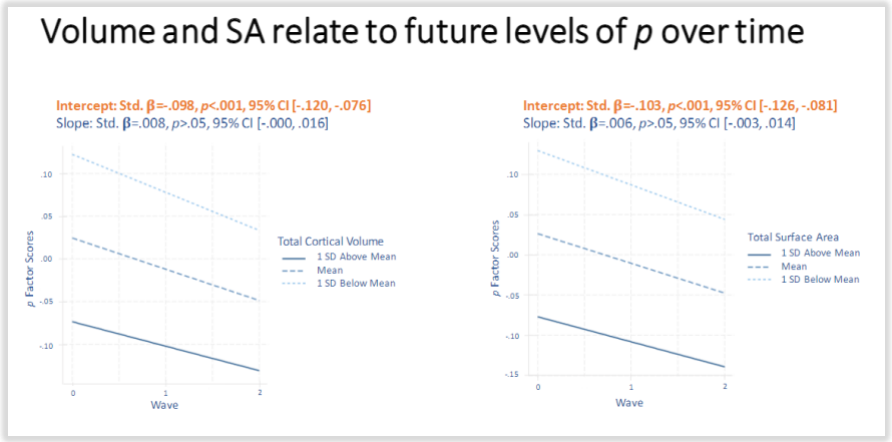
Longitudinal Prospective Relations of Executive Function and Brain Structure with Trajectories of General and Specific Forms of Psychopathology During Preadolescence

Adrienne Romer, Ph.D., Virginia Polytechnic Institute and State University

Dr. Romer explained that high rates of comorbidity exist with mental health disorders, with approximately 50% of individuals who meet criteria for one mental health disorder also meeting criteria for a second. Because of overlap between mental health categories, comorbidity complicates identification of trajectories and unique etiological processes of specific mental disorders. Clinically, comorbidity is associated with greater severity and impairment, as well as more complexity in treatment planning and compliance. One approach to capture the overlap between mental health disorder categories involves factor analytic models that identify transdiagnostic factors such as internalizing, externalizing, and thought disorders, as well as a general psychopathology factor called the *p* factor, which captures shared variation across mental health disorders and accounts for their comorbidity and severity. Individuals with higher *p* factor scores have greater life impairment and symptom severity, more history of childhood maltreatment, more distress, and greater future psychopathology and suicidality. The psychological and neurobiological mechanisms underlying *p* factor are not yet established. The factor may reflect poor executive functioning (e.g., inhibitory control, working memory, and cognitive flexibility), which is associated with many mental health disorders. Imaging has detected structural alterations in brain structure (e.g., volume, surface area, and cortical thickness) associated with *p* factor, and these patterns vary by developmental stage. However, longitudinal studies of the relationship between *p* factor and the brain and neurocognitive alterations are limited. Such studies on preadolescents could be illuminating, as dramatic neurodevelopmental changes characterize this developmental stage, prior to the onset of most mental health disorders.

Dr. Romer has engaged in two related studies with ABCD data to explore whether executive function relates to changes in *p* or specific forms of psychopathology over time and whether childhood brain structure prospectively relates to rates of change in *p* or specific forms of psychopathology over time. Using demographic data, clinical data, parent reports of child behavior, and structural MRI data across three ABCD data-release waves, Dr. Romer and colleagues tested a model of *p* with confirmatory factor analysis to yield a higher-order *p* factor and five intermediate factors: externalizing, internalizing, neurodevelopment, somatization, and detachment. Researchers also tested a one-factor model of executive function, which also fit the data. Analysis showed that poorer executive function at Wave 1 predicts increases in *p* and the five intermediate factors 2 years later. Longitudinal multilevel modeling in the second

study showed that cortical volume and surface area predicted the level of change but not the rate in change in *p* factor scores over time such that lower cortical volume and surface were associated with higher *p* factor scores. Interestingly, the *p* factor scores decreased over time. Evidence suggests that child psychopathology may decrease in preadolescence before rising in adolescence. Finally, cortical thickness was associated with the rate of change of internalizing factors but not *p* factor.



In sum, poorer executive function and smaller total brain volume and surface area may be risk markers for future persistent preadolescent levels of psychopathology. Cortical thinning may protect against increases in internalizing factors but not general psychopathology in preadolescence. Future research may reveal more about the relationship among brain structure and function, executive function, and general and specific psychopathology.

Mapping the Behavioral and Cognitive Profiles of the ABCD Data Set: A Data-Driven Fuzzy Clustering and Graph Theory Approach

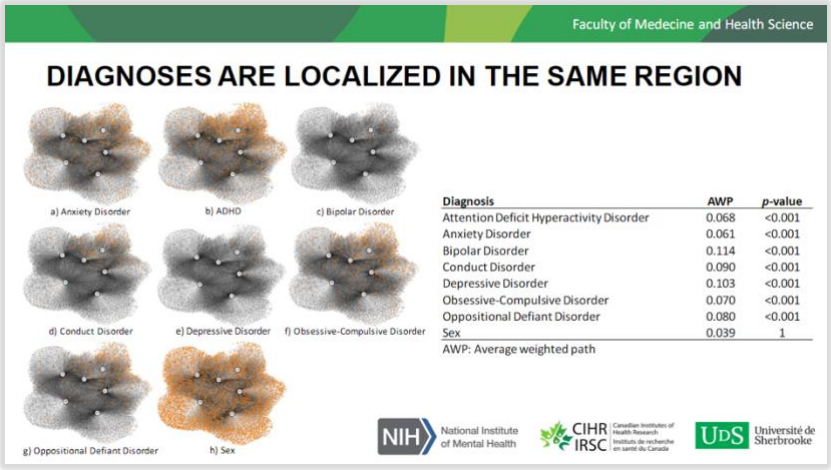
Anthony Gagnon, University of Sherbrooke

Mr. Gagnon began with an electrocardiogram (EKG) analogy. Clinicians use typical and atypical EKGs to inform diagnoses and treatment. He asked whether we could translate this approach to the brain, which can be considered an assembly of electrical signals, though with greater complexity than those of the heart. Visualizing the cognitive and behavioral profile of an individual could similarly inform diagnoses and treatment. Psychiatric considerations (e.g., heterogeneous disorders, comorbidities, evaluations based on criteria in the fifth edition of *Diagnostic and Statistical Manual of Mental Disorders*, and lack of biomarkers) add further complexity to such an approach.

Attention-deficit/hyperactivity disorder (ADHD) affects 7.2% of children and teens, and 10–20% of them do not respond to psychostimulant treatment. In the move toward personalized medicine, evaluating the clinical profile of each patient may help predict treatment response and the risk of developing comorbidities. Mr. Gagnon's work strives to extract cognitive and behavioral profiles from the brain by using fuzzy clustering of ABCD data to obtain a profile of neurotypical children, as well as smaller profiles reflecting diagnosis domains. With this method, subjects can be grouped in multiple clusters at the same time and spatial proximity of the clustering nodes can be measured with a method called average shortest weighted path. Analysis of ABCD data with six cognitive and behavioral variables (working/episodic memory,

* Questions and answers are paraphrased.

executive function/processing speed, verbal ability, internalization, externalization, and stress) yielded six clusters. Clusters 3, 5, and 6 contained the majority of profiles and showed low behavioral scores and varied cognitive scores. Most children with ADHD were in Clusters 1, 2, and 4 with mid to high behavioral scores. Similarly, other diagnoses, such as anxiety disorder, bipolar disorder, conduct disorder, depressive disorder, obsessive-compulsive disorder, and oppositional defiant disorder tended to also be localized in Clusters 1, 2, and 4.

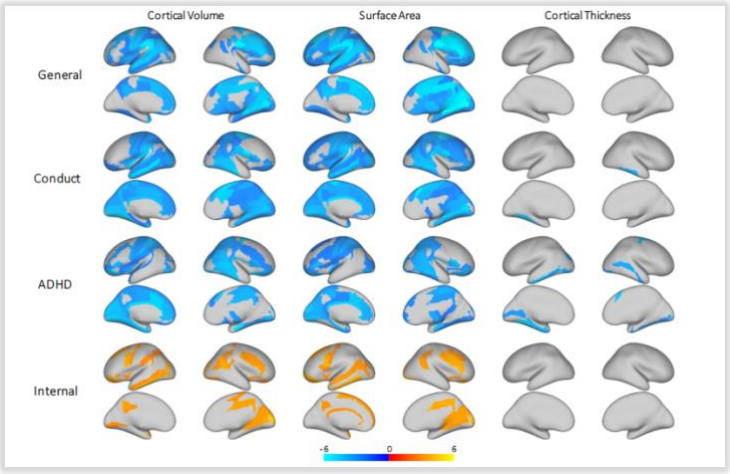


Future work may use this conceptual framework to classify subjects without losing the known heterogeneity within the population, to extract cognitive and behavioral profiles without classifying subjects in boxes, to validate the profiles in an independent cohort, and to evaluate the longitudinal stability of the profiles.

Distinct Patterns of Brain Morphology Associated with Specific Dimensions of Child Psychopathology

Lei Cao, Ph.D., The Ohio State University

ABCD baseline data include T1-weighted scans of brain morphology and data from the Child Behavior Checklist (CBCL) that enable study of mental health from a dimensional perspective. Dr. Cao decomposes CBCL into one general factor and three specific factors (internalizing, externalizing, and thought disorders). Her research examines the associations between cortical morphology and each of these factors from ABCD parent-reported data on 9- and 10-year-old children. A previous study using ABCD data showed a negative association between brain volume and general psychopathology, conduct problems, and ADHD. Dr. Cao and colleagues performed an analysis incorporating brain measures, general factors, conduct problems, ADHD, internalizing problems, age, sex, and other factors.



Results suggest three distinct patterns of association between cortical morphology and different symptom factors. Specifically, general psychopathology and conduct problems are negatively associated with cortical volume. These negative association come from surface area. ADHD is also

* Questions and answers are paraphrased.

negatively associated with cortical volume, but this association comes from surface area and cortical thickness. Finally, internalizing problems are positively associated with cortical volume, coming from surface area. Results are consistent with those of previous studies, and the associations are mostly global. Patterns of surface area and cortical thickness may serve as biomarkers for later-life psychopathology. Future research will extend this work with diffusion MRI and resting-state network data.

Q&A*

Dr. Smith: Thank you to the presenters. These talks complemented one another. Despite using different methods, approaches, and time points, the studies shared some commonalities: associations among decreasing or smaller brain volume, surface area, and psychopathology; the role of executive function or dysfunction in psychopathology; and the complexity and heterogeneity of psychopathology.

Q (in-person participant): Why is surface area a more sensitive measure for psychopathology than cortical thickness for this age group?

A (Dr. Romer): Surface area and volume are most associated with change in general psychopathology over time, whereas cortical thickness is most related to changes in internalizing symptoms. Normative patterns of thickness versus surface area versus volume throughout development may explain this finding. Volumetric changes related to *p* factor are seen in both youth and adult studies. These associations may be driven by surface area in youths, as opposed to thinning in adulthood. Age-related changes may also be a factor, as other studies have suggested.

A (Dr. Cao): Cortical thickness changes are associated with ADHD. However, low surface area and cortical thickness have different genetic origins. Though associated mechanisms are not yet understood, both surface area and cortical thickness contribute to ADHD.

Q (in-person participant): Trends in dimensional psychopathology seem to be improving. This trend holds true for the ABCD cohort in years 3 and 4 of the study (after the COVID-19 pandemic era). How can researchers dissect the sample to find potentially more stratification of trajectories—especially through the pandemic era, associated with substantial psychopathology among children in this age group?

A (Dr. Romer): The decreases are curious, but mental health problems tend to decline in preadolescence and increase during adolescence; detachment symptoms, however, have a slightly increasing trajectory, which could be associated with the pandemic.

Q (virtual participant): What are the effect sizes for associations between brain morphology and psychopathology?

A (Dr. Cao): Please read my forthcoming paper.

* Questions and answers are paraphrased.

Q (virtual participant): Are there any sex differences in regional brain volume, brain thickness, and executive function?

A (Dr. Romer): I controlled for sex as a covariate but did not look at sex as a moderator specifically. Internalizing psychopathology tends to manifest more in females, whereas externalizing psychopathology tends to manifest more in males, which warrants future consideration.

Q (in-person participant): Can we dissect these heterogeneities, patterns, and profiles? How might these patterns translate to clinical settings, particularly in terms of sex, race, ethnicity, and other demographics?

A (Mr. Gagnon): Clinicians can look at behavioral deficits and other deficits in patients rather than trying to apply a label. Clinicians can first look at deficits, second make a diagnosis, and third use the profiles to inform treatment of those deficits.

A (Dr. Romer): Scanning all patients' brains is not practical. Research that identifies potentially causal factors or risk factors may eventually inform transdiagnostic and prevention approaches. For instance, executive function intervention or prevention strategies could prevent or delay the onset or development of a wide range of disorders.

Q (in-person participant): Dr. Cao, did you replicate previous study findings that used only Wave 1 ABCD data?

A (Dr. Cao): I used only Wave 1 data as well but will later use additional data.

Q (virtual participant): Can we incorporate environmental factors into the researchers' models to determine whether environmental factors are better predictors than biological factors?

A (Mr. Gagnon): I plan to incorporate environmental factors into my model to explore some of the cross-cluster groupings I identified.

A (Dr. Romer): Early-life stress and adversity should also be incorporated into these models.

Q (in-person participant): How should we investigate naïve clinical targets—for instance, for patients who have ADHD and are unresponsive to psychostimulant treatment? Other disorders have even worse rates of treatment response. Could Tanner staging influence such investigations?

A (Dr. Romer): I did not explore Tanner staging but acknowledge its potential importance. I controlled for many things but not pubertal status.

Q (Dr. Volkow). Family history of psychopathology represents a risk factor. The ABCD Study captures family history data. Do your models incorporate family history of psychopathology? How might family history relate to disease trajectories and brain measures? Some genes

* Questions and answers are paraphrased.

associated with psychopathology often have transdiagnostic representation. How could associated ABCD genetic information inform research?

A (Dr. Cao): I plan to study maternal psychopathology, maternal medication taken during pregnancy, and children's medication.

A (Mr. Gagnon): I also plan to incorporate maternal psychopathology into my work.

Q (virtual participant): How do SDoH, such as socioeconomic status (SES), affect these models?

A (Dr. Romer): I did not incorporate SES specifically as a moderator in my study, but I did control for the associated factor of parental educational attainment. However, research should consider how early-life environment affects brain and cognitive development and thus later-life mental disorders.

A (Dr. Cao): I incorporated parental educational attainment and family income as covariates. In so doing, I found that associations related to conduct and internalizing problems disappeared, whereas those related to general psychopathology and ADHD remained the same.

Q (virtual participant): Could parent-reported data explain the decreasing trajectories of mental illness? Parents may represent less reliable reporters as children mature into middle and late adolescence.

A (Dr. Romer): Parents tend to be less involved with adolescents as they age, which could influence the accuracy of parent reporting. Using both youth and parent reporting measures would be useful.

Q (virtual participant): Is it possible that higher baseline *p* factor scores stem from the nature of the questions asked to participants? Baseline questions ask about children's lifetime symptoms, whereas follow-up questions ask about symptoms since the most recent evaluation.

A (Dr. Romer): That's a possibility.

A (in-person participant): Some studies show that parent-reported CBCL data suggest improvement over time, which may reflect actual improvement and/or an increasing lack of parental knowledge of the covert antisocial behavior and covert emotions of older adolescents. The ABCD Study should incorporate as many youth-reported data as possible, particularly regarding covert psychopathology.

Scientific Data Session #3: Health Disparities (Moderator: Deborah Linares, Ph.D., National Institute on Minority Health and Health Disparities Division of Integrative Biological and Behavioral Sciences)

Dr. Linares briefly introduced herself and the speakers**.**

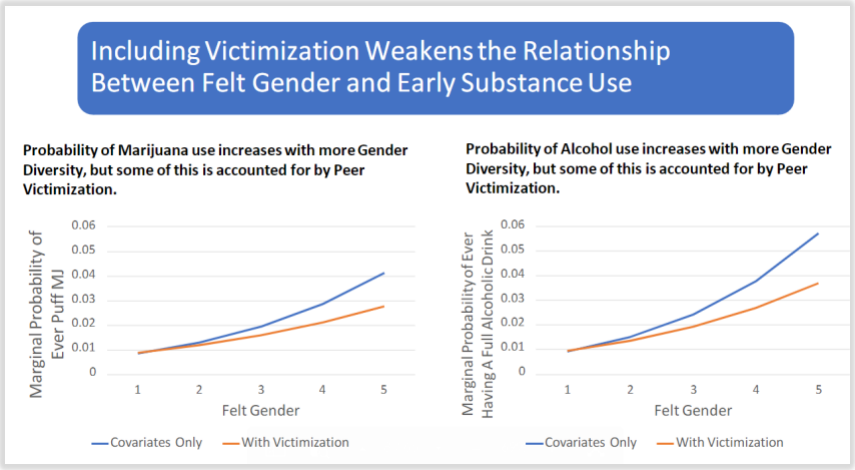
* Questions and answers are paraphrased.

Adolescent Gender Diversity and Substance Use: A Mediating Role of Peer Victimization

Annabel Diestel, University of Vermont

Previous research has identified health disparities among transgender and gender-diverse adults and adolescents. For example, transgender youths have elevated rates of suicidal ideation. Greater gender diversity among youths has been associated with parent-reported behavioral and emotional problems. Ms. Diestel defined "gender identity" as one's internal sense of self and one's definition of one's own gender. She said that "transgender" is an umbrella term describing individuals whose gender identity does not align with their sex assigned at birth and that "gender-diverse" is a term characterizing variation from societal expectations about male and female gender norms. Ms. Diestel's research seeks out the drivers of early-life substance use among gender-diverse populations.

It is important for studies of gender-diverse youths to avoid pathologizing gender diversity by incorporating minority stress/chronic stress models, acknowledging systemic risk of discrimination and victimization, and identifying and examining potential protective factors to mitigate adverse outcomes. The ABCD Study gathers gender identity data and uses the two-step method (i.e., asks about both sex assigned at birth and current gender identity) among other survey questions and measures (e.g., felt-gender scores). ABCD data show that gender diversity increases with age, most likely reflecting maturing youths' increasing understanding of their gender identity.



Gender-diverse adolescents are at greater risk for substance use. The researchers examined whether peer victimization partially explains the relationship between felt-gender scores and early substance use. Although felt-gender scores, overall substance use rates, and peer victimization rates were low (as expected for the 12-to-13-year-olds in question), statistical analysis showed significant correlations between higher felt-gender scores and early substance use, as well as between felt-gender scores and peer victimization. Including victimization in the substance use analysis weakens the association between felt gender and early substance use.

Results suggest the importance of considering gender diversity when analyzing community samples and how some health disparities among gender-diverse youths, such as those related to substance use, may be partially explained by peer victimization. Ms. Diestel acknowledged two study limitations: the small portion of participants reporting any substance use and the single time point considered in the analysis. Future study may examine substance use patterns as the ABCD cohort ages; may consider protective factors such as activity involvement,

* Questions and answers are paraphrased.

creativity, emotional regulation strategies, community support, and resilience; and may help to inform future interventions.

Social Determinants of Health and Child Mental Health, Cognition, and Physical Health: A Data-Driven Approach Using ABCD

Yunyu Xiao, Ph.D., Weill Cornell Medical College

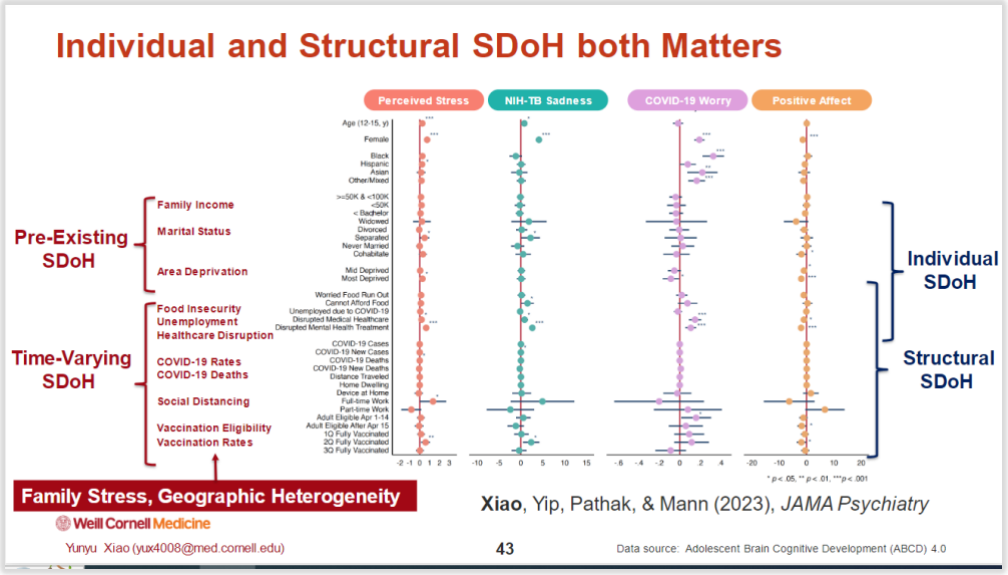
Mental health disparities associated with race/ethnicity, sex, sexual orientation, SES, and their intersection persist, particularly for minoritized racial and ethnic groups, such as high rates of suicidality among Black youths. Similarly, researchers have identified mental health disparities by sex, sexual identity/orientation, and gender identity, and these disparities intersect with race. Geographic disparities, pandemic-related factors, life course factors, and other sociodemographic influences further complicate suicidal trajectories. Although research to date has identified these sociodemographic disparities, few studies have considered environmental factors and the mechanisms driving these demographic differences. In sum, there is a gap in the literature and empirical evidence base on the SDoH associated with mental health disparities.

SDoH include all conditions related to where people are born, live, work, learn, play, worship, and age. SDoH also include education, health care access, neighborhoods and built environments, economic stability, and the social and community context (per the categories established by the Healthy People 2030 project). Compared with the more robust bodies of empirical evidence associated with suicidality and genetics, epigenetics, early-life adversity, and psychological conditions, data on SDoH and suicidality are lacking. Reviewing the literature reveals that most studies have used limited individual, small-set, or cherry-picked SDoH variables and do not reflect a more comprehensive consideration of SDoH. Dr. Xiao recommends three solutions to rectify research gaps and inform prevention efforts.

First, researchers can identify SDoH clusters associated with mental, cognitive, and physical health with machine learning techniques. Dr. Xiao's study considered 84 SDoH variables in seven SDoH domains (bias, crime and drugs, social context, SES, natural environment, physical and health infrastructure, and education). Her research yielded four SDoH patterns: affluence, high-stigma environment, high socioeconomic deprivation, and high crime and drug sales. Indexing these four patterns against children's mental, physical, and cognitive outcomes showed differential associations. For instance, high socioeconomic deprivation is associated with poor mental and cognitive health, and children in high-crime and high-drug-sale environments tend to have higher body mass indices (BMIs) and greater incidence of sleep disorders.

* Questions and answers are paraphrased.

Second, researchers can model multilevel SDoH. For instance, during the pandemic, rates of COVID-19 infection and associated deaths were disproportionately high among Black communities, Latinx communities, other communities of color, low-income families, and those in deprived areas. A comprehensive understanding of SDoH is necessary for researchers to illuminate these and other health disparities. Modeling both individual and structural SDoH with ABCD data reveals differential trajectories of mental health Publications by Dr. Xiao and colleagues propose a framework for modeling multilevel SDoH not only at the individual level but at the structural level, which identifies differential trajectories of mental health.



Dr. Xiao concluded by briefly discussing the third solution, which pertains to the relationship between policy and SDoH. Dr. Xiao's research shows that policies related to COVID-19 affected children's mental health. She called for future research to consider SDoH comprehensively, for greater attention to subgroup differences, and for consideration of SDoH to inform policy.

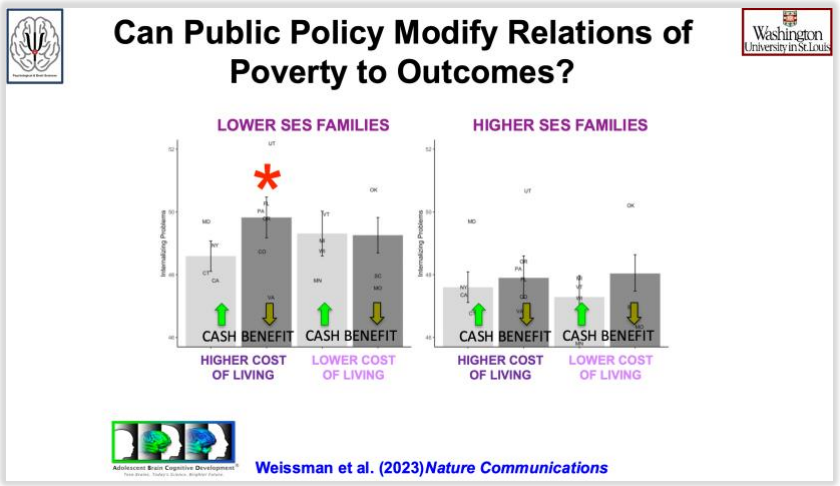
The Enduring Impact of Poverty on Risk for Mental Health Challenges in Youth
Deanna Barch, Ph.D., Washington University in St. Louis
Overwhelming evidence indicates that childhood poverty and neighborhood adversity can lead to chronic stress, disruptions in caregiver support, and exposure to environmental toxins, all of which challenge health and development in children. More specific studies consider how these challenges affect development of brain structure, function, and connectivity, which can give rise to greater risks to brain health, including mental health challenges, substance use, educational challenges, and cognitive challenges. Dr. Barch described one such study that used ABCD data and linked early poverty with mental health challenges and brain development differences. She then discussed how the unique ABCD data set enables researchers to ask questions about how public policies can help mitigate some of the negative effects of early poverty.

Dr. Barch presented data on the income-to-needs ratio (calculated by dividing a family's total household income by the Federal poverty threshold for a family of the same size) in relation to internalizing problems such as depression and anxiety, indicating an association between lower SES and higher internalizing problems. Similarly, lower SES and income-to-needs ratio scores are associated with lower hippocampal volumes in adolescents of middle school age. Some findings suggest that hippocampal volume and connectivity can mediate the effects of early-life poverty on internalizing symptoms.

* Questions and answers are paraphrased.

Individual families' experiences influence children's development, but neighborhood disadvantage also affects development. Although neighborhood disadvantage relates to the SES of the families living in a given neighborhood, structural inequities and structural racism can preclude families from minoritized racial and ethnic groups from moving to higher-income neighborhoods. Thus, the Area Deprivation Index also proves informative and suggests that neighborhood deprivation—more than factors such as family income and caregiver educational attainment—is associated with child outcomes such as worse memory, worse executive function, worse reading skills, worse vocabulary skills, worse processing speed, and more severe externalizing symptoms. Data overwhelmingly support the effects of neighborhood deprivation on child cognitive and mental health outcomes.

Biological factors such as hippocampal and prefrontal cortex size can mediate the effects of neighborhood deprivation. In addition, public policies can modify the relationship between poverty and outcomes. ABCD data are collected from multiple sites in multiple states and thus enable comparison of the effects of regional public policies. The relationship between poverty and child health outcomes varies from state to state. Analyses incorporating income and policy factors such as the income-to-needs ratio, the cost of living, state-issued cash benefits to families experiencing financial challenges, and Medicaid expansion point toward differential outcomes. For instance, among children from families with low SES in states with high costs of living, those in states with higher cash benefits had larger hippocampal volumes and fewer internalizing problems than those in states with lower cash benefits. Researchers found similar results in high-cost-of-living states with higher and lower degrees of Medicaid expansion.



In sum, poverty and deprivation can have long-lasting effects on the brain and increase risk for brain health challenges. Childhood poverty is a public health crisis. Early detection and intervention can mitigate risks, and researchers should develop interventions for mediating mechanisms.

Q&A*

Dr. Linares: Health disparities are complex, and researchers and clinicians must consider individuals within their environments, especially at critical developmental stages. This type of research benefits from multiple theoretical approaches and linked data sets and from looking beyond categories of only race or ethnicity to understand the causes and pathways to develop new methods of prevention and intervention to reduce disparities and disease burden. Policies and interventions can address structural disparities and SDoH.

* Questions and answers are paraphrased.

Q (Dr. Linares): Which protective factors should ABCD researchers explore?

> A (Ms. Diestel): I hope to examine activity involvement and community cohesion as potential protective factors, particularly for sexual and gender minority populations. Family support and legislative support are possible protective factors.
>
> A (Dr. Xiao): I recommend exploring adolescents' social networks, including family members, friends, and neighborhoods. Social media can also represent a protective factor. Though research has focused on the risks of youth social media engagement, social media can also have beneficial protective factors and social support, particularly for minoritized populations.
>
> A (Dr. Barch): I recommend studying resilience factors such as familism and different levels of support—family-level, peer-level, and community-level—and how these factors may differ by race and ethnicity.

Q (Dr. Volkow): What is needed to understand the complex social network structures that affect children's health? How can researchers collect associated data?

> A (Dr. Barch): Researchers should collect data on where and with whom youths spend time (e.g., peers, immediate family members, extended family members, unofficial caregivers). Researchers need to expand the information on school-related activities to better understand children's social support and sources of resilience.

Q (virtual participant): Ms. Diestel, when were ABCD's data on sex and gender collected by the two-step method?

> A (Ms. Diestel): These data were collected in the Year 3 follow-up.

Q (in-person participant): How should we discuss SDoH without pathologizing minority status, low SES, or regional identities? How should we communicate these findings to policymakers?

> A (Dr. Barch): It's a challenge to address the needs and urgency of childhood poverty issues without pathologizing poverty. I advise addressing concerns with policymakers in terms of long- and short-term investment. Most social interventions have considerable costs but save resources in the long term. We need to discourage short-term thinking and encourage policymakers and others to consider long-term benefits and savings. Involving health economists can help.

Q (virtual participant): Dr. Xiao, why did you choose standard cluster analysis instead of another technique?

> A (Dr. Xiao): Other options had less potential. The literature shows that SDoH are measured by one or two variables or by clustering. Clustering incorporates more

* Questions and answers are paraphrased.

variables and helps us to communicate with policymakers more effectively and to encourage them to allocate resources toward addressing SDoH to yield better outcomes.

Q (virtual participant): How does neighborhood deprivation differ in urban and rural areas?

A (Dr. Barch): ABCD data do not represent many rural areas, where access to health care is limited (an important SDoH). Also, environmental exposures tend to be different in urban and rural areas (e.g., air pollution versus agricultural runoff).

Q (virtual participant): Can we study the economic efficacy of state cash benefits on brain health?

A (Dr. Barch): Researchers with areas of expertise other than mine could do so with access to electronic health records. Such studies could be illuminating.

Q (virtual participant): What is the mechanism through which poverty affects hippocampal volume?

A (Dr. Barch): The animal literature suggests that deprivation probably affects gene expression. One hypothesized mechanism involves methylation of glucocorticoid receptors and the brain's response to and ability to shut down the hypothalamic–pituitary–adrenal axis.

Q (in-person participant): Were ABCD children who chose "I don't understand the question" in response to questions about gender identity and being transgender included in the percentages of gender-diverse ABCD individuals (0.5% of 9-to-10-year-old ABCD participants and up to 3% in the oldest group)?

A (Ms. Diestel): ABCD children who responded "I don't understand the question" were not considered "gender-diverse" in my analysis, though I incorporated data on those responses in my study. The increase in ABCD participants answering that they are transgender or gender-nonbinary over time most likely stemmed from the fact that older children have a better understanding of their gender identities.

Responsible Use Panel Discussion (Moderator: Elizabeth Hoffman, Ph.D., Associate Director, ABCD Study)

Dr. Hoffman made brief introductory remarks about responsible use of ABCD Study data and about how ABCD Study data are being used with expansive and multidisciplinary approaches. Addressing bias and stigma in science will counter historical trends that have served to narrow scientific insight. Historically, most scientific study has focused on individual-level contributors to health and behavior. As the previous session on SDoH emphasized clearly, researchers need to incorporate more complex contributors, modifiable factors, systemic and structural factors, and other considerations into research. ABCD researchers have developed innovative

* Questions and answers are paraphrased.

approaches for incorporating contextualizing variables into longitudinal designs, including geospatial methods for mapping individual-level data to external data sets to capture built and natural environmental factors, as well as analytic approaches for modeling data to provide context for interpreting brain–behavior associations. Panelists will discuss these topics, as well as community-engaged research strategies.

Carlos Cardenas-Iniguez, Ph.D., University of Southern California
Dr. Cardenas-Iniguez discussed considerations for using participant-level linked data sets. He referred meeting participants to his paper describing ABCD Study data, including environmental and policy-related variables, and the associated rationale. In this paper and his talk, Dr. Cardenas-Iniguez made recommendations for using linked external data (LED) data for exploring SDoH and other considerations. He cautioned that researchers should use these data appropriately and responsibly, particularly to avoid perpetuating stigma or harm. First, the ABCD Study includes many variables, measuring deprivation in many ways. Researchers should review the metadata to understand the spatial and temporal coverage of the data before making analyses and interpretations. Second, with so many variables, researchers should consider a theoretical or framework-informed approach to determining which variables are appropriate for their models. Variables may overlap, exist redundantly, or be completely different, and researchers should select them thoughtfully. Third, researchers should think about the effect of structural racism on all of these data. All variables exist in a sociopolitical context and should be presented as such. Some variables are associated with noise. Others are very coarse measures. Researchers must take the responsibility to reflect that in their analyses and reporting, be transparent, and spell out the limitations of the data. Fourth, LED data reflect larger, neighborhood- or state-level influences, and researchers should not use them to make individual-level inferences. Finally, the ABCD Study releases derived data based on residential addresses, but ABCD doesn't release those addresses. Thus, if researchers are linking data to ABCD data, those researchers should keep in mind that some participants live far from the sites where data are collected. Dr. Cardenas-Iniguez advised researchers to be mindful of this fact in making geospatial inferences and to report all study limitations.

Amy West, Ph.D., Children's Hospital Los Angeles and the University of Southern California
Dr. West discussed ethical considerations in working with data from Native communities, as the ABCD Study includes data on Indigenous youths. She discussed some of the historical background of how U.S. Indigenous populations have been subjected to 500 years of colonization, actual and cultural genocide, and marginalization. After contact with Europeans, Native populations dropped from an estimated 10-20 million individuals to fewer than 500,000 because of genocide, warfare, and disease. Federal policy shifted from one of eradication of Native populations to one of assimilation, relocation (i.e., the reservation system), and cultural indoctrination (e.g., Indian boarding schools). Colonization can be considered an SDoH. Researchers should think intergenerationally about SDoH, and understand that intergenerational trauma can last for decades or even centuries.

* Questions and answers are paraphrased.

Representation can mitigate this intergenerational SDoH. The ABCD Study sample includes approximately 400 Indigenous youths, a roughly representative population sample. However, Dr. West's quick literature review suggested that about 90% of papers published with ABCD Study data have not reported on Native participants and have limited their analyses to White, Black, Asian, and Hispanic racial/ethnic categories. Dr. West encouraged researchers to report on Native participants in studies using ABCD data and to form authentic partnerships with Indigenous representatives, tribal leadership, and other Native stakeholders. Research benefits from community participation methodologies, operationalizing such methods, and including Native voices in creating and telling the stories their data yield. Otherwise, data can be used in reductionist, deficit-based, and/or abusive ways that perpetuate harmful narratives. Indigenous communities can have a more resilience-focused, holistic, and relational way of understanding things than Western science. Through authentic partnerships and by incorporating some of this understanding into scientific research, we can take genuine strides toward a more social, relational understanding of how factors relevant to ABCD intersect. Intergenerational and historical trauma (an important social determinant of health in Indigenous populations) becomes apparent in rates of mental health inequities and other health outcomes, such as high rates of obesity and diabetes stemming in part from the loss of traditional agricultural methods and Federal programs distributing unhealthful food commodities—such as sugar, flour, and lard—to reservation residents.

Danilo Bzdok, M.D., Ph.D., McGill University

Dr. Bzdok discussed precision medicine and population stratification in brain–behavior associations. First, precision medicine, at its core, differs completely from Western 20th-century biomedicine, which concentrates on group differences. Traditionally, intervention efficacy is tested by comparing its effects among different groups. Although this binary thinking has led to improvements in medicine, precision medicine takes a different approach. It posits that although a particular intervention works for many people, it does not work for every individual in a group. Precision medicine concerns itself less with group contrast and more with the individual patient in front of a health care provider. Precision medicine uses large data sets such as ABCD to make precise conclusions and predictions for individual patients. Many researchers make the mistake of thinking that prediction models and machine learning paradigms are statistical tools, akin to those used in hypothesis testing and more traditional biomedical research. Prediction models and machine learning paradigms have nothing to do with *P* values and statistical significance (i.e., the tools that helped researchers develop clinical guidelines).

Second, major sources of population stratification—what some people call subgroups—are associated with very subtle effects. In some areas of medicine and biology, these effects are easier to study. However, thousands of genes inform cognitive dimensions or aspects of brain structure and function. The kinds of effects that cognitive neuroscientists, psychologists, and mental health researchers are trained to hunt are difficult to study. In many studies, factors other than those considered by the research question—for instance, forms of background variation—may be driving the effects of the study unbeknownst to the researchers. In

* Questions and answers are paraphrased.

neuroscience, the effects of background variation may be larger than the effects of interest considered by the research questions. Large data sets from more general populations have fewer exclusion criteria, greater representation, and more inclusivity and thus increase the amount of background variation beyond historical laboratory norms.

Third, these problems have emerged only recently with the advent of data sets such as ABCD and the UK Biobank. Researchers lack adequate quantitative analysis toolkits to incorporate the depth and breadth of covariates (e.g., age, sex, and SES) that are now available. Researchers need to develop appropriate analytical tools for the rich background variation in the ABCD cohort and other large data sets.

Discussion*

Q (Dr. Hoffman): How can researchers foster a culture change at the level of reviewers, editors, and journal publishers to ensure responsible data use?

> A (Dr. Bzdok): My team has recommended guidelines for what researchers using prediction models should report in their papers.
>
> A (Dr. Cardenas-Iniguez): I recommend the instructions in my paper and other published guidelines (e.g., guidelines from the National Academies of Sciences, Engineering, and Medicine) for responsible data use and reporting.
>
> A (Dr. West): As a clinical scientist and intervention scientist, I have seen a growing understanding of what it means to do authentic community engagement in developing interventions, though much room for improvement exists.

Q (Dr. Volkow): Although we want researchers to report on data obtained from American Indians/Alaska Natives, doing so can prove challenging because of resistance from tribal leadership. How can we improve inclusion efforts? Also, Dr. Bzdok, how should we address your point about background effects and how the background signal related to scanner type can be larger than all other information contained in the image? Can subgrouping data sets distinguish the information of interest from the background variation? What recommendations do you have for study designs that will yield replicable results and avoid the background problem?

> A (Dr. Bzdok): A recent unpublished study in my laboratory incorporated major sources of population stratification and considered their connotations. This phenome-wide analysis of ABCD data included the totality of the behavioral variables and tried to identify the coherent components or patterns in the entire cohort across thousands of families and phenotypic indicators that drive variation across families. We found that, of the five major sources of population variation, four have strong associations with dozens of SES variables. (ABCD files indicate that there are approximately 200 SES variables in the ABCD data.) Thus, although SES constitutes a major driver of variation across the families, these SES effects are not the same in each of these four driving components. Therefore, I recommend aggressively data-driven analyses of the phenome

* Questions and answers are paraphrased.

of the ABCD cohort. When studies identify sources of population stratification, researchers must adapt their analysis paradigms to incorporate diversity factors. Unfortunately, researchers cannot rely on established deconfounding techniques, which cannot remove the entirety of the confounding signal. Researchers need to use other techniques (e.g., propensity scores and horizontal integration of tools) more common to epidemiology than to neuroscience.

Q (virtual participant): Dr. West, how do you reconcile ABCD's five-level race/ethnicity variable (i.e., White, Black, Hispanic, Asian, and multiple/other) with your recommendations to better address population diversity?

A (Dr. West): Disaggregate the "other" category. Although it is impractical to represent the over 500 Indigenous tribes, I recommend disaggregating the Indigenous U.S. population from the "other" category in research.

Q (in-person participant): What is the cultural and genetic overlap between the Hispanic population and Indigenous populations?

A (Dr. West). I'm uncertain whether or how the ABCD Study distinguishes between Hispanic people and Indigenous people. There is wide variation within the experiences and genetic backgrounds of Indigenous and part-Indigenous populations in the U.S., Canada, Mexico, and Central America.

Flash Talk Session #1 (Moderator: Dana Greene, Ph.D., NIH Office of Behavioral and Social Sciences Research)

Quantifying Environmental and Functional Brain Network Contributions to Children's Current and Future Cognitive Abilities

Arielle Keller, Ph.D., University of Pennsylvania

Human brains develop in unique, complex environments, and we have unique brain network organizations that result in unique ways of thinking and individual differences in cognition. Poorer youth cognition is associated with poorer adult cognition and health outcomes, and adverse childhood experiences and environmental disparities can affect both cognition and functional brain function networks. Dr. Keller's research takes a personalized neuroscience approach to link multidimensional experiences and environments with personalized functional brain networks and individual differences in cognition. Her study applied a bifactor analysis to 354 environmental variables to define a single latent dimension, the exposome, which encompasses structural inequalities. Analysis showed that scores from individual cognitive tasks and latent cognitive dimensions were significantly associated with the exposome across all cognitive domains and across all samples, at baseline and at the 2-year follow-up.

Dr. Keller then asked how the exposome variable relates to brain network organization. To avoid the limitations of the classical approach to brain mapping, Dr. Keller's personalized medicine approach uses a technique called non-negative matrix factorization, enabling identification of person-specific brain networks at scale. She identified 17 personalized

* Questions and answers are paraphrased.

functional networks, which are associated with differences in youth cognition. She created a model to test how functional brain organization predicts exposome scores and tested this model with cross-validation. Her model showed strong correlation between predicted and actual exposome measures, suggesting that functional brain organization reflects the exposome. Further, functional brain networks that vary the most across individuals are most affected by the environment.

Q&A*

Q (virtual participant): Does the exposome include environmental measures such as particulate matter?

> A (Dr. Keller): Some measures of environmental toxins are incorporated in ABCD, but I am not aware of the details on particulate matter.

Q (virtual participant): Are there ways to assign weights to the exposome to understand which aspects contribute the most to the brain and cognition?

> A (Dr. Keller): The model captures specific features of children's environments, some of which are more strongly associated with specific aspects of cognition. However, the strongest association exists between the overall exposome score and all dimensions of cognition.

Characterizing the Relationship Between Cortical Gradients and Cognitive Traits in Children

Mia Zwally, NIMH Intramural Research Program

The ABCD Study strives to understand how circumstances and experiences affect cognitive development. Previous research had identified a relationship between functional connectivity and behavior with canonical correlation analysis; thus, Ms. Zwally chose to explore this relationship further with cortical gradients, which embed functional connectivity in a whole-brain hierarchy, and determine whether individual differences in cortical gradients relate to variations in behavior and cognition.

Ms. Zwally's analysis of fMRI data from ABCD participants involved creating gradients with the BrainSpace toolkit and comparing ABCD child gradients with adult gradients. Previous research had established differences in child and adult gradients in the order of variance contribution. Ms. Zwally's results were consistent with those of previous research. Next, Ms. Zwally and colleagues conducted statistical analyses on gradient similarity values and behavioral/cognitive scores. Results were inconclusive. In sum, this study's ABCD cortical gradient findings aligned with previous work but did not establish a significant relationship between gradient similarity values and behavior/cognition.

* Questions and answers are paraphrased.

Pubertal Development Shapes Intrinsic Functional Brain Network Correlates of Working Memory

Mackenzie Mitchell, University of North Carolina at Chapel Hill

Working memory is essential for cognition and relies on functional connections between frontoparietal and cingulo-opercular networks (and other brain networks). On the population level, adolescence marks a period of rapid improvement in working memory. Using multiple types of fMRI scans and pubertal development scale data from ABCD, Ms. Mitchell conducted a brain network analysis, with particular attention on the frontoparietal and cingulo-opercular networks. She characterized high and low segregation between pairs of networks. She found that pubertal status shapes how network segregation relates to changes in working memory—with functional segregation more or less advantageous to the development of working memory, depending on pubertal stage and pubertal tempo. In cases of slowly progressing puberty, frontoparietal segregation from higher-order cognitive and auditory networks promotes greater improvement in working memory.

Q&A*

Q (in-person participant): What was the range of pubertal status in the study?

> A (Ms. Mitchell): Pubertal stage was measured numerically on a scale of 1 to 4, and participants ranged from approximately 1.19 to just above 3 at baseline.

Q (virtual participant). What was the sex of the study population, and how did you define pubertal tempo?

> A (Ms. Mitchell): The sample included boys and girls. I ran the analysis for girls only and boys only. I found that the results from the girls-only sample looked similar to those of the mixed-sex sample, but results from the boys-only sample differed from the results presented (most likely because the typical age of onset of male puberty meant that the ABCD data captured only a small range of male pubertal values). Tempo was defined by the difference between pubertal scores divided by the change in age in months.

From Reactive to Proactive Control: Neural Development of Inhibitory Control

Zhiyao Gao, Ph.D., Stanford University

Inhibitory control involves both proactive processes (i.e., preparation of strategic responses in advance when increased control is anticipated) and reactive processes (i.e., inhibiting prepotent responses when interference occurs). Theories suggest that children use more proactive control and than reactive control with maturation, but the neural mechanisms underlying this shift have been poorly examined. Dr. Gao's study used single-trial estimation (LSS) and representational similarity analysis to examine the developmental change of neural coding underlying proactive and reactive control. After detailing the experimental study design using the Stop Signal Task, Dr. Gao presented multiple results of his study. Compared with baseline, at the 2-Year follow-up, children show (1) less neural coding of reactive control, (2) greater neural coding of proactive control, and (3) a stronger influence of neural coding of proactive

* Questions and answers are paraphrased.

control on stop signal reaction time (an index of inhibition speed). These findings demonstrate a systematic developmental shift in brain activation patterns during inhibitory control.

Q&A*

Q (in-person participant): How was proactive control quantified?

> A (Dr. Gao): These numbers were measured at the neural level during the go trials.

Q (Dr. Volkow): What was the range of correlation between the individual measures and the group measures?

> A (Ms. Zwally): I don't know. I did not want to skew my observations by studying that range.

Q (virtual participant): Ms. Mitchell, why did you choose the emotional trials in the *n*-back scans instead of the non-emotional trials?

> A (Ms. Mitchell): I used both. It would be interesting to parse the two. My logic was to include as many trials as possible to get the most stable measure of working memory.

Q (Dr. Volkow): How is the onset of puberty also a function of race (in terms of related measures of stress and poverty)? How do we best factor such considerations into studies on puberty?

> A (Ms. Mitchell): I included both race and a measure of SES as covariates but did not parse them specifically.
>
> A (Dr. Keller): The exposome variable in my study encompassed the totality of features such as stress and poverty.

Q (in-person participant): Dr. Keller, did you look at pubertal markers as part of the exposome?

> A (Dr. Keller): No.

Q (virtual participant): Could differences in the association with environmental factors across different networks simply be a matter of lower variance leading to poorer association?

> A (Dr. Keller): This was less of a confounding factor. The networks that are plastic for the longest period of time are the ones most influenced by the environment. Thus, unsurprisingly, the networks that vary most across individuals are the ones most influenced by the environment.

Day 1 Closing Remarks

Dr. Murray closed the day with thanks to Dr. Volkow, the poster presenters, the speakers, and all participants. She also shared logistical information about the next day's meeting.

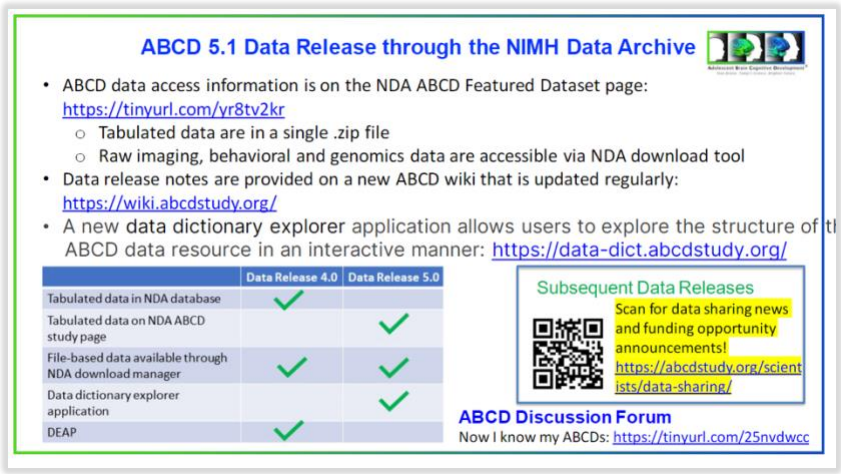
* Questions and answers are paraphrased.

Day 2 Welcome & Opening Remarks

Dr. Murray welcomed all participants and thanked the poster presenters and those who participated in mentoring sessions. She shared logistical details, including instructions for providing feedback on the meeting, and encouraged meeting participants to network.

Overview of ABCD Study Resources

Elizabeth Hoffman, Ph.D., Associate Director, ABCD Study
Kimberly LeBlanc, Ph.D., Scientific Program Manager, ABCD Study



Dr. Hoffman described the ABCD Study's open science model and its roughly annual data releases. Each annual release includes previously released data amended with quality corrections where needed. In addition, fast-track raw neuroimaging data are released on an ongoing basis. Currently, data include everything up to the Year 3 follow-up, along with partial Year 4 follow-up data. Currently, NIH offers four funding opportunities for secondary analyses of ABCD Study data: RFA-DA-22-037, RFA-DA-22-038, PAR-22-137, and PAR-22-138. The ABCD Study also provides several new data resources, including a Wiki that includes regularly updated release notes, general information, and domain-based information, a data dictionary explorer explaining what is available within the ABCD Study database, and a discussion forum. In the summer of 2024, NIH will release the 6.0 data set, which will appear not on the NIMH Data Archive (NDA) but on a new data sharing platform. The new platform will require users to submit new data use agreements.

Dr. LeBlanc described the NBDC Biospecimen Access Program, which enables internal and external investigators to apply to use residual ABCD biospecimens, including saliva, teeth, sera, and DNA from saliva or whole blood. Biospecimens are available for studies consistent with ABCD Study objectives and studies aiming to expand the knowledge of child or adolescent health. Researchers can use the PAR-23-229 X01 mechanism to apply for biospecimens but will need outside funding to support analyses and sample shipment. The application process involves reviewing and exploring available

* Questions and answers are paraphrased.

biospecimens, submitting an inquiry, having the inquiry reviewed, obtaining funding, and then submitting an application. The NBDC Biorepository Portal houses information relevant to the application process, details of the biospecimen collection, a biospecimen explorer enabling users to filter and search the biospecimen collection, answers to frequently asked questions, and additional details.

Q&A*

Q (in-person participant): Can rejected X01 applications be revised and resubmitted?

A (Dr. LeBlanc): Yes.

Q (virtual participant): Must data collected from these biospecimens be uploaded to the NBDC Biorepository Portal and made available to other researchers?

A (Dr. LeBlanc). Yes.

Special Session: Scientific Training in Addiction Research Techniques (START) Program (Moderator: Micah Johnson, Ph.D., University of South Florida)

Dr. Johnson introduced three scholars from START, a transdisciplinary program for early-career investigators. The program has been designed to diversify perspectives in the ABCD Study community.

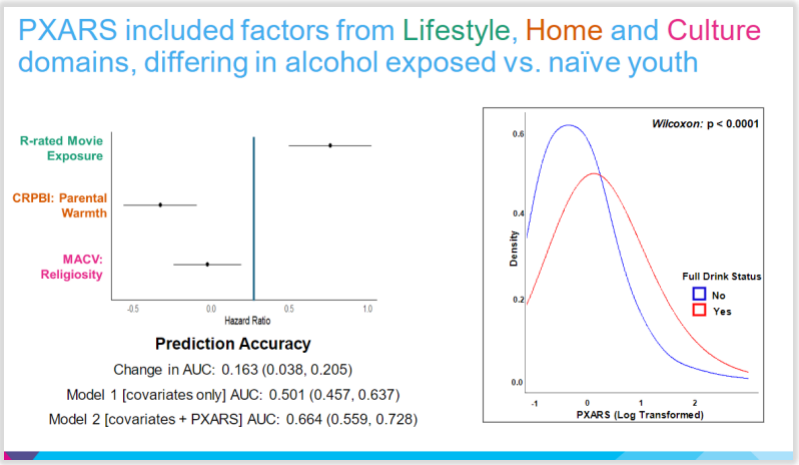
Unveiling the Cumulative Impact of the Environment on Alcohol Use Onset: Deriving PolyeXposure Alcohol Risk Scores (PXARS) for Youth in the ABCD Study

Faith Adams, Icahn School of Medicine at Mount Sinai

Alcohol is the most common and often the first psychoactive substance used by youths. Although alcohol use among minors is at a historic low—with only 6% of eighth graders reporting previous-30-day alcohol consumption in 2022—concerns about underage use persist. Alcohol use disorder (AUD) affects approximately 10% of young adults, and early-age onset of use increases risk of AUD. Risk factors for alcohol use onset and AUD include family history of alcoholism, polygenic liability, and environmental risk factors such as low parental monitoring, low school engagement, neighborhood stressors, and cultural norms. Research gaps persist because many genetic studies have focused on participants of European descent and therefore have limited generalizability, because there has been a lack of focus on age of onset, and because many studies have had a selective approach to environmental risk factors. Data-driven strategies enable a systematic study of nongenetic environmental factors, and use of exposome-wide association studies (ExWAS) can enable researchers to capture the contributions of several exposome variables and interexposure correlations.

* Questions and answers are paraphrased.

Ms. Adams' work has developed PXARS to capture individual-level exposure risk factors for alcohol use onset independent of genetic factors. Her study aims to evaluate the exposomic associations with youth alcohol use onset from ExWAS data and to derive PXARS to assess the additive and cumulative risks for alcohol use onset.



Ms. Adams reviewed her methodology, including use of ABCD self-reported data on age of first drink and ABCD exposome data (including information on lifestyle, parental health, culture, and home, neighborhood, and school environments). She used these data and statistical methods to develop a model, informed by ExWAS, to derive PXARS.

ExWAS identified 15 exposomic features (e.g., discrimination, screen media activity, adverse home environment, and parental psychopathology) independently associated with time to alcohol use onset. The PXARS multivariate model included factors across multiple domains, such as R-rated movie exposure, the religiosity subscale from the Mexican American Cultural Values Scale (MACVS), and parental warmth. Prediction accuracy with these variables increased by 16%, suggesting that incorporating environmental factors increases prediction accuracy (though doing so was less accurate in the alcohol naïve group). Limitations of the study include underestimation of underserved racial and ethnic populations, measurement error, and recall bias. Future studies may consider how PXARS compare with genetic risk factors and explore the neurobiological correlates for alcohol use onset in youths.

Familism Values and Child Self-Regulation in the ABCD Data Set

Rick Cruz, Ph.D., Arizona State University

Dr. Cruz's research focuses on cultural variability—including factors such as familism, an aspect of cultural identity—in relation to child outcomes. Research often treats race and ethnicity as proxies for culture. His work involves population subgroups and moderation analysis. He hopes to bridge the mainstream and multicultural literature on developmental psychopathology.

Dr. Cruz also cautioned about the cultural misattribution bias, which can prompt researchers to focus on cultural analysis for minoritized populations and to assume that culture is absent or not meaningful for "majority" populations. Both longitudinal and cross-sectional data suggest that familism values (among Latinx families and other groups) are generally related to lower substance use risk. Definitions of self-regulation vary but generally include the ability to regulate behavior, attention, and affect. Self-regulation—as measured by the UPPS-P model of impulsive personality, which looks at five dimensions of impulsive behavior (namely, negative urgency, lack of premeditation, lack of perseverance, sensation seeking, and positive urgency)—is associated with less early substance use initiation, fewer substance use problems,

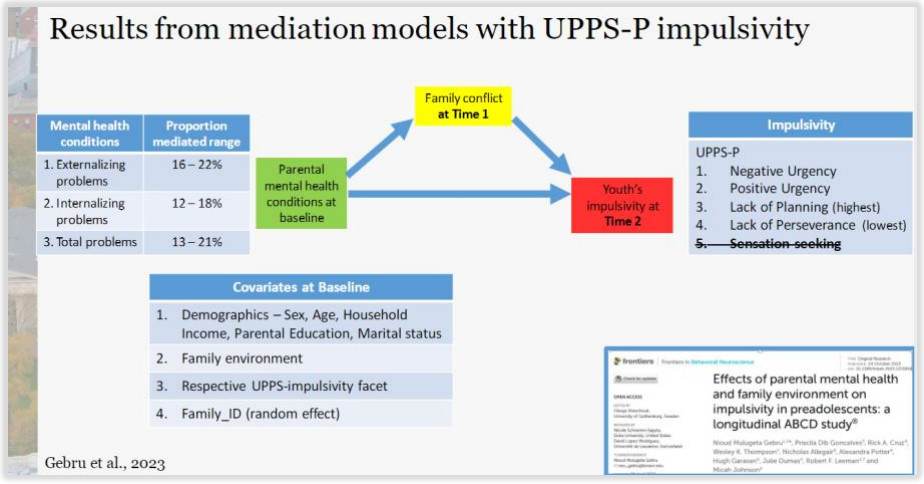
* Questions and answers are paraphrased.

and more positive life outcomes. Few studies consider the relationship between familism values and self-regulation.

Dr. Cruz studies the direct and moderated associations between culture (particularly parent–child familism values and how they vary by race and ethnicity) and self-regulation. Dr. Cruz briefly reviewed his methodology of analyzing familism-related ABCD data, other ABCD data, UPPS-P scores, and MACVS data. His early findings suggest that (1) familism seems to be a risk factor for white youths in particular in terms of greater sensation seeking and lack of premeditation, (2) models of lack of perseverance did not appear to converge appropriately, (3) familism seems to be a protective factor for minoritized youths in terms of negative urgency (but this effect dissipates for Black youths), and (4) familism seems to be a risk factor for Black youths in particular in terms of positive urgency. These findings also illustrate the potential value of examining cultural factors in the context of race/ethnicity when studying child self-regulation.

The Effects of Parental Mental Health and Family Conflict on Youth Impulsivity
Neo Gebru, Ph.D., Brown University
Dr. Gebru discussed how family environment mediates relations between parental mental health conditions and youth impulsivity. In particular, although the field has established that parental mental health conditions affect child outcomes, the mechanism is not understood. Impulsivity is a multifaceted construct characterized by a rapid response to stimuli and is associated with substance use, sexual and other risk behaviors, and other deleterious health outcomes. The literature suggests that maternal depressive symptoms predict increases in adolescent delay discounting (an aspect of impulsivity) and adolescent substance use.

Dr. Gebru's research focuses on how parental mental health conditions increase family conflict, which in turn increases youth impulsivity. Dr. Gebru used statistical methods to analyze baseline, 1-year follow-up, and 2-year follow-up data on parental mental health (e.g., externalizing, internalizing, and total problems), family conflict and environment, and behavioral inhibition system (BIS) and behavioral activation system (BAS) measures. Though effect sizes were small, Dr. Gebru's analysis found that family conflict mediated the effect of parental baseline externalizing problems on youth impulsivity measured by scores related to fun seeking on BIS/BAS scales (but not youth impulsivity measured by scores related to reward



* Questions and answers are paraphrased.

responsiveness or drive) at 2-year follow-up. The analysis revealed a similar pattern for effects of parental total problems at baseline on youth impulsivity at the 2-year follow-up.

Dr. Gebru concluded by stating that consistent with previous studies on maternal depression, his study found that difficult family functioning as an intergenerational mechanism creates an important social context for youth development. Further, effective family interventions could improve outcomes for families with high levels of conflict.

Q&A*

Dr. Johnson: Programs such as START are essential in promoting interdisciplinarity, innovation, diverse perspectives, and consideration of processes and social contexts that drive substance use trajectories.

Q (virtual participant): Ms. Adams, did you encounter any exposomic risk factors not accounted for in your study?

> A (Ms. Adams): The ABCD Study did a great job of collecting many environmental measures. However, I'm concerned that these measures were collected at different time points, which complicated consideration of baseline measures in my analysis. As a result, peer alcohol use was excluded from my study. Also, ABCD data do not reflect some cultural factors that I wanted to explore.

Q (in-person participant): Dr. Cruz, did you incorporate different cities in your analysis?

> A (Dr. Cruz): Site location was a covariate in the study. However, factors such as ethnic density could also influence results. I also incorporated immigrant status in the analysis. Some communities in common immigrant destinations (e.g., Miami, Los Angeles, and New York) may serve as buffers of stress for new immigrants.

Q (in-person participant): Ms. Adams, did you include race/ethnicity as a control variable in your analysis? Would race/ethnicity be better considered part of the exposome?

> A (Ms. Adams): Although race/ethnicity is not an exposome factor per se, the exposome incorporates other measures—such as some of the geocoded measures—that are inflected by race/ethnicity. Future analyses could incorporate race/ethnicity into the exposome.

Q (in-person participant): Ms. Adams, did you differentiate between types of screen media use in your analysis?

> A (Ms. Adams): My study included data from all of the questions on the ABCD screen time questionnaire, including questions about hours of screen time, exposure to R-rated movies and video games, and other factors. Exposure to R-rated movies was the significant variable.

* Questions and answers are paraphrased.

Q (in-person participant): Ms. Adams, is it better to apply PXARS across or within subgroups?

> A (Ms. Adams): Many of those decisions were guided by the limitations of the participant sample and the ABCD data, which present challenges for powering analyses focused only on non-White participants.

Q (virtual participant): How might different types of parental mental health issues mediate family conflict differently?

> A (Dr. Gebru): My analysis with UPPS-P data found differences between internalizing and externalizing parental problems. However, analysis with BIS/BAS scales showed that most of the effect was seen with externalizing problems. These findings suggest that externalizing problems, such as aggression, probably influence family conflict more than internalizing problems, such as anxiety and depression.

Q (in-person participant): How might parental genomic influences be separated from parental environmental influences on child outcomes?

> A (Dr. Gebru): I like that idea but would have to collaborate with other experts to control for parental genetics.

Q (in-person participant): Could home environment function as a potential protective factor against negative youth impulsivity or other outcomes?

> A (Dr. Gebru): I like that idea, but I'm unsure whether ABCD data include home protective factors as variables. However, family cohesion is an ABCD variable and could function as a moderating influence (though not a causal factor).

Q (in-person participant): Dr. Gebru, could you explain the time lag in the mediation analysis? Were you trying to capture time-related causal effects?

> A (Dr. Gebru): Yes, I was trying to capture how baseline parental problems influence later youth impulsivity. However, running the tests cross-sectionally, I found that the results hold.

Q (virtual participant): Ms. Adams, did you consider the moderating and additive effects of environmental factors?

> A (Ms. Adams): Yes, researchers can use PXARS, such as polygenic risk scores, to look at mediating effects on impulsivity. With so many ABCD variables and so many different types of risk factors for alcohol use onset, researchers can use PXARS data to explore mediating, moderating, and additive effects.

* Questions and answers are paraphrased.

Lunch Session: "Ask the ABCD Experts" (Moderator: LCDR Traci Murray, Ph.D., MPH, RN Scientific Diversity Advisor, ABCD Study, NIDA)

Topic: Non-Imaging Protocol
Panelist: Susan Tapert, Ph.D., University of California, San Diego
Facilitator: Diana Alkire, Ph.D., Program Analyst, ABCD Study, NIDA

Topic: Imaging
Panelist: Damien Fair, Ph.D., University of Minnesota
Facilitator: Janani Prabhakar, Ph.D., Program Officer, HBCD Study, NIDA

Topic: Health Disparities Research
Panelist: Carlos Cardenas-Iniguez, Ph.D., University of Southern California
Facilitator: Kim LeBlanc, Ph.D., Scientific Program Manager, ABCD Study, NIDA

Topic: Data Exploration and Analysis Portal (DEAP)
Panelist: Janosch Linkersdörfer, Ph.D., University of California, San Diego
Facilitator: Elizabeth Hoffman, Ph.D., Associate Director, ABCD Study, NIDA

Topic: Biostatistics
Panelist: Wesley Thompson, Ph.D., Laureate Institute for Brain Research
Facilitator: Katherine Cole, Ph.D., Acting Director, Scientific Program Manager, HEALthy Brain and Child Development (HBCD) Study, NIDA

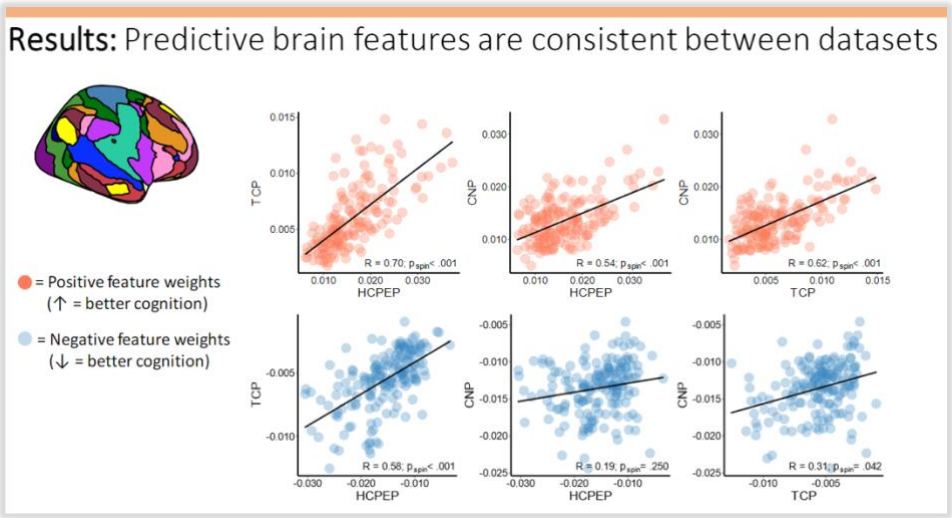
Scientific Data Session #4: Novel Analytic Uses of ABCD Data (Moderator: Angela Laird, Ph.D., Florida International University)
Dr. Laird commented on the progress the ABCD Study has made since its inception in late 2015, and she introduced the speakers.

Metamatching: Translating Prediction Models from Large to Small Data Sets
Sidhant Chopra, Ph.D., Yale University
Dr. Chopra began by explaining the utility of predicting phenotypes in patients. Doing so helps to account for variability within and between diagnostic categories; provides individualized estimates of current and future traits, states, and behaviors; complements explanation; and enables computational and algorithmic advances in data science. Accurate and stable prediction models rely on large data sets such as the ABCD and UK Biobank data sets. Other considerations include how the brain has massive redundancy and degeneracy and how signals associated with one behavior may correlate highly with those of many other behaviors.
As such, with access to large data sets, researchers do not need to build predictive models from scratch. Instead, researchers can use the metamatching framework to use correlations from

* Questions and answers are paraphrased.

large data sets to boost predictions in smaller samples. The framework includes (1) building a prediction model and training a machine learning model with the large data set, (2) using the trained model to make predictions on a phenotype of interest in a smaller clinical sample (and examining correlations between health/behavioral data and the variable of interest and then selecting the best correlation to use in the prediction model), and (3) training a new model to make predictions based on these health and behavioral data.

Researchers used this framework on small clinical fMRI data sets from the Human Connectome Project for Early Psychosis, the Transdiagnostic Connectomes Project, and Consortium for Neuropsychiatric Phenomics. Metamatching yields accurate and significant predictions surpassing those of traditional models. Metamatching also develops models that can make accurate predictions with new data sets, suggesting generalizability. An updated metamatching framework involves using multiple large data sets to inform the predictive models. In sum, leveraging information from large sets of population data can boost predictions in smaller psychiatric samples, and these models generalize between independent data sets.



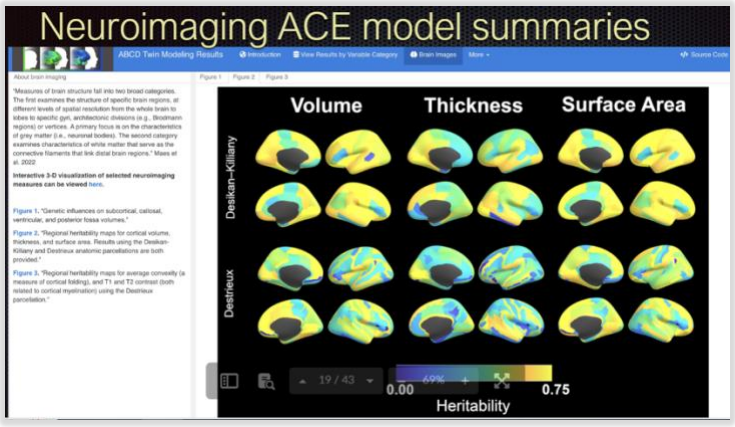
Twin Analyses: New Developments for ABCD

Michael C. Neale, Ph.D., Virginia Commonwealth University

Dr. Neale opened by encouraging meeting participants to study structural equation modeling, which is superior to standard regression methods. His talk focused on new methods useful for ABCD work, including estimating variance components instead of paths, testing for gene–environment (GE) covariance, testing for GE interactions, testing causal hypotheses, and conducting longitudinal analyses.

* Questions and answers are paraphrased.

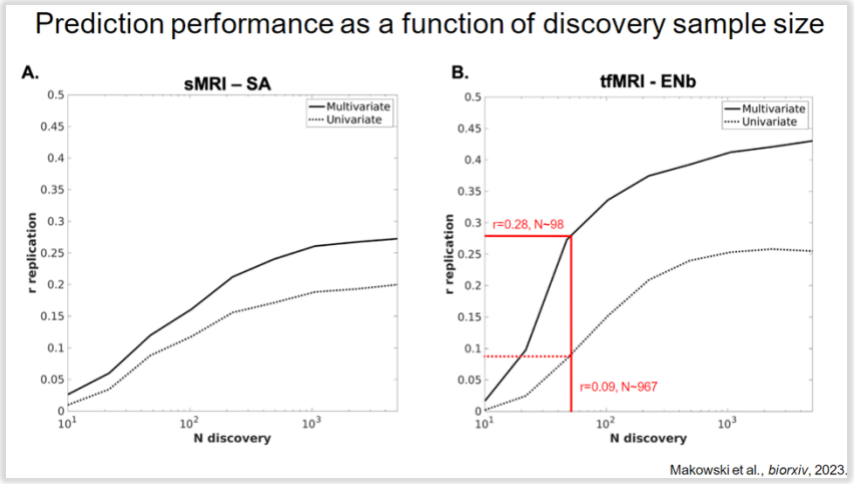
Dr. Neale outlined the benefits of estimating variance components instead of path coefficients in twin studies; the variance component approach can yield negative values, suggesting unexpected results. Researchers applied the variance component approach to 55,000 ABCD continuous variables and created an associated database.



GE covariance approaches can involve study of polygenic scores, longitudinal data, and untransmitted alleles (i.e., alleles not inherited from parents), which can help detect environmental transmission. These approaches can illuminate sibling, environmental, and parental effects. Dr. Neale emphasized the importance of testing causal hypotheses (e.g., an endophenotype causing SUD), determining the direction of causation, and using bidirectional causal hybrid models.

Longitudinal data are also useful. Adding polygenic risk scores to cross-lagged panel models allows differentiation between contemporaneous and lagged causal effects and permits estimation of optimal assessment intervals.

The Big and the Small of It: Leveraging the ABCD Study for Prediction in Smaller Samples
Carolina Makowski, Ph.D., University of California, San Diego
Dr. Makowski established some context for her presentation by reviewing recent concerns about the reproducibility and effect sizes of brain–behavior associations with MRI data, including the claim that "thousands of individuals" are needed for brain-wide association studies. She also described how research has historically limited predictions of behavior to one or two imaging modalities and univariate methods. Dr. Makowski released a preprint article exploring whether studies are powered to predict cognition reproducibly in baseline ABCD data with a subset of data with multiple imaging modalities beyond resting-state fMRI (e.g., vertex-wise structural/diffusion MRI and task-based functional MRI with different trials), with multiple measures (e.g., cortical surface area, cortical thickness, intracortical-restricted isotropic diffusion, and white matter–restricted directional diffusion), with multivariate methods, and/or in a region of interest–agnostic manner. Researchers compared multivariate and univariate predictions of cognition. Unlike univariate



* Questions and answers are paraphrased.

methods, multivariate methods enable detection of patterns or distributed patterns of effects across the brain.

Study results suggest that reproducible brain–behavior associations can be measured with multivariate methods—not only in large data sets, such as ABCD, but also in smaller replication samples at the core of many existing grants. Also, even with as few as 50 subjects in discovery samples, replication samples of approximately 100 subjects can adequately power multivariate approaches to predicting general cognition with task-based functional MRI data. This research may allay stakeholder concerns that thousands of subjects are necessary for brain-wide association studies.

Q&A*

Q (in-person participant): The twin component of the ABCD Study has been underutilized. How can the community encourage researchers to use these data on twins?

> A (Dr. Neale): Workshops on methodology and broader education on ABCD data use and models of interest could increase enthusiasm for the twin component.

Q (in-person participant): Many large data sets are not enriched for clinical populations. Does this fact affect how new training models benefit from the larger samples?

> A (Dr. Chopra): I agree that models improve when the training data set includes phenotypes that match what the model is designed to predict. Multilayered metamatching boosts predictive power by effectively enriching the training data set.

Q (in-person participant): Could you give us some additional details on using polygenic scores with cross-lagged longitudinal models? Could Dr. Neale's approach apply to non-twins?

> A (Dr. Neale): The longitudinal models include random effects and can be used with non-twin data. However, with twin-related data, these models most likely are more informative. A recent paper explains that including instrumental variables in this regression reveals not only cross-lag associations but also within-occasion variables mutually causing one another. This effect is sometimes lost in studies with too much time between assessments.

Q (virtual participant): Dr. Makowski, could you explain multivariate models versus univariate models?

> A (Dr. Makowski): Univariate modeling involves taking a single voxel and associating it with differential statistics associated with a behavior of interest. Multivariate modeling uses thousands of vertices or hundreds of regions of interest and feeds them into a prediction algorithm. Multivariate modeling takes patterns into account, not just one variable at a time.

* Questions and answers are paraphrased.

Q (virtual participant): What are the best approaches for estimating GE effects?

> A (Dr. Neale): Researchers have only approximate measures in the form of polygenic scores and limited information on environment. As such, longitudinal twin modeling is probably the best approach.

Q (in-person participant): Can we leverage ABCD data for smaller studies via a polyvertex score or something similar in which researchers train the weights (analogous to a polygenic score in genetics)? This process would be complicated with task-oriented fMRI, which is designed to elicit a specific type of cognitive response.

> A (Dr. Makowski): Perhaps different types of MRI data could work well for new studies on working memory and other cognitive functions.

Q (virtual participant): What are the concerns related to corrections for multiple testing with structural equation modeling in ABCD data?

> A (Dr. Neale): Sometimes multiple testing is not helpful. Research has shown that correcting for multiple testing can overemphasize certain features. Effect sizes are probably more important.

Q (Dr. Volkow): What is the optimal imaging modality for predicting behavior? How might researchers use artificial intelligence (AI) to incorporate information from all subjects into predictive models? For instance, AI could render a synthetic image derived from information on (resting) functional connectivity, structural morphology, and other features.

> A (Dr. Makowski): I used multivariate methods separately to inform my predictions, but methods currently in development use a multimodal fusion to make predictions. Interpretation of those multimodal fusions or synthetic images and determining which features are important might prove challenging.

Q (Dr. Volkow): Multimodal clinical assessments would be impractical, but clinical practice could benefit from algorithms developed from multimodal or synthetic image–informed predictive models.

> A (Dr. Chopra): I recommend optimizing predictive models from longitudinal data before developing predictive models for clinical applications.

Flash Talk Session #2 (Moderator: Bethany Deeds, Ph.D., NIDA Division of Epidemiology, Services and Prevention Research)

Indicators of Environmental Disadvantage and Their Associations with Delay Discounting
Julia Felton, Ph.D., Henry Ford Health
Environmental disadvantage encapsulates multiple factors that affect youth development at the individual, family, and community levels. Poverty affects decision-making by decreasing cognitive capacity, narrowing choices, and focusing attention on solving immediate problems

* Questions and answers are paraphrased.

rather than long-term planning. Dr. Felton's research focuses on delay discounting—that is, prioritizing short-term solutions over long-term benefits, a trend associated with substance misuse, obesity, gambling, and other risky or unhealthy behaviors involving short-term appetitive rewards. The literature suggests that delay discounting can be an important mediator between disadvantaged environments and risky behaviors.

Dr. Felton's analysis used inclusive measures of disadvantage and a measure of delay discounting to identify environmental features most influential on rates of delay discounting. She found that the community-level factors had the greatest influence on rates of delay discounting, consistent with previous results. However, these effects were attenuated when youths perceived their neighborhoods to be safe and supportive. This research could inform policies to foster healthy decision-making.

Increasing the Representation of Minoritized Youths for Inclusive and Reproducible Brain–Behavior Associations

Jivesh Ramduny, Ph.D., Yale University

Responding to the lack of inclusivity in neuroscientific research on humans, Dr. Ramduny's research seeks ways to maximize inclusion of data from high-motion minoritized youths in data sets related to population neuroscience and to generate inclusive, reproducible brain–behavior associations from those typically excluded from studies. ABCD data collection processes have been more inclusive than disciplinary norms. However, a tension exists between sample sizes and head motion; that is, a greater number of minoritized youths are excluded because of strict head motion thresholds to improve fMRI signal quality. Retaining only ABCD data from low-motion youths disproportionately reduced the sample sizes of Black and Hispanic youths, to about half of their total samples.

Dr. Ramduny tested a more inclusive bagging framework, taking 100 scrubbed time points from four 5-minute fMRI runs from all participants to yield usable fMRI data from more than 99% of Black, White, and Hispanic participants. This framework was tested to determine whether these 100 scrubbed time points were sufficient to examine brain–behavior associations. Findings showed that the data were usable and could be meaningfully interpreted. The differences in brain–behavior associations identified with the bagging approach and the standard approach were small when the high-motion youths were included. Results suggest that the bagging approach enhances sample representation for testing brain–behavior associations and helps to fulfill the promise of population neuroscience data sets to produce generalizable effect sizes across a diverse population.

Improving Accuracy and Precision of Heritability Estimation in Twin Studies: Reassessing the Measurement Error Assumption

Gang Chen, Ph.D., NIMH Intramural Research Program

Twin studies enable researchers to predict heritability by partitioning variability in traits, variability in environment and culture, and variability in genes. The ACE model of estimating heritability uses values reflecting additive genetics (A), shared environment (C), and nonshared environment (E). Dr. Chen discussed special cases when this classical model proves

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problematic—for instance, for some cases of within-individual variability. In such cases, estimates improve with hierarchical modeling estimation (HME) models, which create hierarchies of data that can account for things such as intra-individual variability. Dr. Chen discussed his validation process with simulations and the results of comparing the predictive capacity of HME versus ACE models with ABCD data.

Dr. Chen concluded that the ACE model does not accommodate measurement errors and is associated with problems of underestimation and other statistical difficulties. HME, however, captures the data-generating mechanism, provides accurate narrow-sense heritability estimations, and adheres to causal inferences. His study provides many lessons that could inform future modeling research.

Relationships Between BrainAGE and Maturational Metrics in Early Adolescence
Lucy Whitmore, University of Oregon
The brain age gap estimate (brainAGE) measures the gap between apparent brain age predicted by a model trained on neuroimaging data and actual brain age. BrainAGE, developed to study older populations and Alzheimer's disease, has recently been applied to the study of depression, anxiety, and adversity in adolescent populations. Ms. Whitmore's research applied an existing model trained on a sample of 9–19-year-olds to ABCD baseline and 2-year follow-up data. She then trained her own models on ABCD baseline and 2-year follow-up data and applied them to held-out ABCD data.

Ms. Whitmore found that brainAGE positively relates to pubertal development (assessed with youth and parent reports) in early adolescence. BrainAGE has an unclear relationship to cognition in early adolescence. The brainAGE measure may capture some aspects of biological maturation but not necessarily aspects of other domains. Future studies may expand this research to a wider age range and may use longitudinal data.

Brain Dynamics and Energy Landscapes in Children with ADHD
Marie Hedo, Weill Cornell Medical College
Ms. Hedo studied ADHD by examining structural and functional imaging data, fluctuations and transitions in brain activity during rest, and baseline ABCD data through the lens of network control theory. Ms. Hedo and colleagues calculated transition energy (TE), the minimum energy required to transition from one of four intrinsic brain states to another. Researchers compared TE levels for a group of 2,365 boys and girls with and without ADHD. A secondary principal component analysis examined a subgroup of 98 ABCD participants with ADHD for comorbidities (e.g., externalizing and internalizing symptoms, internalizing symptoms only, or no comorbid symptoms).

Overall, girls had higher TEs than boys at the global level and at some regional and network levels. Among girls but not boys, ADHD is associated with higher TE in subcortical, temporal, and frontal areas. The principal component analysis found that having ADHD and internalizing symptoms is positively associated with TE in the frontoparietal network areas and the limbic network areas. Having ADHD but no comorbidities is positively associated with TE in the limbic

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network. At the regional level, higher principal component scores positively correlate with TE, and different regional patterns exist for each profile.

The results suggest a sex-dependent association between TE and ADHD. Increases in TE in limbic network areas may relate to difficulties in emotional processing and regulation. Energy landscapes differ between different general psychopathological symptom profiles.

Q&A*

Q (in-person participant): Is sampling 100 MRI frames sufficient to measure connectivity?

> A (Dr. Ramduny): I tested 100 scrubbed time points against the full data set and found that 100 time points produced meaningful results. There is no one-size-fits-all standard for the number of time points. I chose 100 time points to maximize inclusion and sample size. However, after testing the bagging framework across data sets, behaviors, and other factors, I am convinced that it works.

Q (in-person participant): How was brainAGE calculated? Ms. Whitmore, did you control for the effects of puberty in your cognition analysis?

> A (Ms. Whitmore): brainAGE was calculated from cortical volume, cortical surface area, and subcortical volume. Estimating the age of an individual's brain carries many implications. For the purposes of my work, I examined brainAGE as it relates to cognition apart from developmental progress. This approach most likely has utility for policy, science communication, and other areas.

Q (Dr. Volkow): ADHD symptoms change with age. Although ADHD is more prevalent in boys than in girls, TE was higher in girls. Ms. Hedo, did you differentiate between inattention and hyperactivity, which is a more prevalent symptom in boys and decreases with age?

> A (Ms. Hedo): I considered distinguishing ADHD symptoms—such as inattention, hyperactivity, and impulsivity—in my analysis and differentiating by age.

Q (Dr. Volkow): Some developmental neuropsychologists postulate that in high-stress conditions, development is accelerated. If so, what should researchers expect to see in images of apparently older-age brains?

> A (Ms. Whitmore): In older individuals, Alzheimer's symptoms and other problems are almost always associated with older brainAGE than actual age. However, in adolescents, some symptoms are associated with younger brainAGE, and others with older. For instance, depression is associated with an older predicted brainAGE, but anxiety is associated with younger predicted brainAGE. Accelerated brain development cannot be identified from cross-sectional brain imaging data. More research might clarify these developmental and symptom time tables and predictions.

* Questions and answers are paraphrased.

Day 2 Closing Remarks

Dr. Murray ended the inaugural AIIM by thanking all presenters, attendees, organizers, contractors, and NIH staff members. She encouraged attendees to submit feedback on the meeting.

Dr. Dowling thanked all meeting participants, particularly Dr. Murray, and stated that the AIIM panel and poster presenters demonstrated the value of the ABCD Study and proved the critics of the ABCD Study wrong. Dr. Dowling reiterated Dr. Murray's request to meeting participants to submit feedback to inform subsequent meetings.

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