PREFACE

ABCD Behavior Genetics: Twin, Family, and Genomic Studies Using the Adolescent Brain Cognitive Development (ABCD) Study Dataset

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Human development reflects ongoing and continuous biological and functional change in multiple systems and at varied scales, and the variability in human phenotypes arises from complex additive and interactive effects between individual genomes and variation in physical functioning, social relationships, and cultural environments (Jernigan et al. 2018). Although development occurs from the prenatal period well into older adulthood, adolescence is seen by many as a particularly important developmental period. Adolescence is a sensitive period of brain development characterized by heightened neural plasticity (Casey et al. 2014; Luciana 2013), and is a time of rapid physical, cognitive, emotional, and social changes, as well as increasing independence and responsibilities (Arnett 2011). For many adolescents, this is also a time of increases in highly rewarding but risky behaviors, including substance initiation and use (Substance Abuse and Mental Health Services Administration, 2023), and rates of various forms of psychopathology increase rapidly during adolescence and into adulthood (Costello et al. 2011; Kessler et al. 2005; Powers and Casey 2015). Thus, the importance of investigations during the adolescent period for understanding individual and contextual contributors to both adaptive and maladaptive development is widely recognized.

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Adolescent Brain Cognitive Development (ABCD) Study

The Adolescent Brain Cognitive Development (ABCD) Study developed out of the recognition of the importance of understanding brain, physical, social, and mental health during adolescence. The overarching aim of the ABCD Study is to provide to the scientific community an informative, high-dimensional open data resource that defines the range and pattern of variability in trajectories of brain and behavioral development during adolescence, and allows for the estimation of influences of a range of potential risk and protective factors for adolescent development, including psychosocial contributors, and the onset and progression of substance use and mental health disorders. To meet this overarching aim, the ABCD Study has enrolled > 11,000 youth and their parents/caregivers at 21 sites located across the United States to develop a study sample designed to approximate the sociodemographic characteristics of the United States population (Garavan et al. 2018). Youth were first assessed at age 9/10 years, and prospectively assessed at regular 6-month to 1-year follow-up assessments (through age 19/20 years). Assessments are multimodal, comprehensive, and include extensive and repeated assessments of brain structure and function, neurocognition, psychosocial functioning, physical health, substance use, and mental health, as well as contextual factors, including culture and environment. As of this writing, youth are currently completing their age 15/16-year assessment, and data from the first three years of assessments (i.e., through the two-year follow-up assessment) have been released to the scientific community in Data Release 4.0.

In recognition of the fundamental role of genetics, in addition to environments, for human variation and development, the ABCD Study also includes genetically informative design components, including the family study design, nested twin subsample, and assessment of genetic data—genome-wide single nucleotide polymorphism (SNP)

genotype data from DNA samples provided by the participants. Youth and their parents/caregivers were enrolled, along with eligible siblings, and 860 same-sex twin pairs were enrolled as part of the ABCD Twin Hub (Iacono et al. 2018). Genetic data were also collected from youth in saliva and blood samples, which were subsequently genotyped and made available to the scientific community for genome-wide association studies (GWASs) (Uban et al. 2018). By including these genetically informative design components, in addition to its many other design strengths, the ABCD Study extends knowledge to be gained and increases causal inference in new and exciting ways—as we highlight here in this Special Issue.

Aims of the Special Issue

In this Special Issue, we introduce the genetically informative design components of the ABCD Study, and some of the ways that researchers are beginning to use these in behavior genetic research. We provide a brief overview of the multiple ways in which the ABCD Study offers the scientific community a unique and invaluable opportunity to address fundamental questions about human development, adolescent brain and behavioral development, and the range of individual and contextual factors that contribute to adolescent adjustment and well-being. We also seek to highlight some of the important work being done by researchers with the ABCD Study genetics data, including application of both classic biometric models, causally informative analyses, and state-of-the-art genetics approaches. Finally, we hope to encourage researchers to take advantage of this unique, large-scale, longitudinal, comprehensive, and genetically informative open data resource to address new questions regarding adolescent development, with the ultimate goal of preventing or mitigating negative outcomes and promoting adolescent well-being.

Papers in the Special Issue

We have brought together in this Special Issue a collection of papers that leverage the genetically informative ABCD Study data. The papers can be roughly divided into those that use the twin family data in biometric and causal modeling approaches, and those that use the genetic data. Although published shortly before this Special Issue, we include in this overview the paper by Maes et al. (2023), which provided initial estimates of additive genetic, shared environmental, and nonshared environmental variance in a wide range of measures collected at the age 9/10 year baseline ABCD assessments. In addition to providing evidence

of the heritability of imaging, neurocognitive, mental health, and anthropomorphic indicators, the authors also provide an open access, interactive online tool that can be used by researchers to generate twin correlations and estimates of genetic and environmental variance in >50,000 continuously distributed brain and behavioral phenotypes collected in the ABCD Study. This online tool is available at: https://abcdtwinhub.shinyapps.io/baselineTwinResults/ This is an invaluable resource for the scientific community in answering basic questions about the relative contributions of genetic and environmental influences to adolescent brain and behavioral phenotypes, and serves as an important jumping off point for multivariate analyses that allow for further testing of hypotheses related to the direction of causation.

To facilitate the use of the genetically informative ABCD Study data, Fan et al. (this issue) provide a comprehensive overview of the genetic data available in the ABCD Data Releases. In this paper, Fan et al. provide detailed descriptions of the population structure of the ABCD sample (which includes genetically related and unrelated singletons, nontwin siblings, twins, and their parents/caregivers), and relevant genetics research to date, processing procedures of the genotyping data (quality controls and imputations), allele frequency distributions, and some recommendations on using genetically derived instruments. Smith et al. (this issue) provide an elegant example of a new approach using the Fast Efficient Mixed Effects Analysis (FEMA) package that leverages both the twin family and genetics data in the ABCD Study. Incorporating both family structure and SNP-derived genetic relatedness using this approach allowed for more precise heritability estimates for neurocognitive functioning in the full ABCD Study sample of singletons and twins. These papers highlight the usefulness of current established approaches to genetics data in the ABCD Study, as well as the potential to develop and apply state-of-the-art methods to answer important questions about human variation and development with greater precision.

Although it is now well established that essentially all aspects of human behavior are genetically influenced to at least some extent (Polderman et al. 2015; Turkheimer 2000), by allowing for estimation of genetic and environmental influences, the ABCD Study genetics data also offers key insights about the importance of the environment for adolescent development. Gustavson et al. (this issue) found that variance in music listening, exposure to musical instruments, and instrument playing/singing at age 9/10 years was primarily accounted for by shared environmental influences. In contrast, Watts et al. (this issue) found that variance in subcortical gray matter microstructure and volume was primarily accounted for by genetic influences, as well as high genetic stability from age 9/10 years to age

11/12 years. Dash et al. (this issue) examined GxE effects, finding that higher neighborhood adversity, lower educational opportunity, and life stress were associated with increased environmental influences, whereas other aspects of life opportunities were associated with increased genetic influences. Rader et al. (this issue) used both classic biometrical models and a causally informative co-twin control approach, finding that variance in pain at age 12/13 years was primarily accounted for by shared and nonshared environmental influences, and that associations between pain and psychopathology were primarily due to shared environmental influences, except for externalizing problems, which may have a potentially causal effect on pain. Collectively, these papers highlight the relevance of the ABCD Study for answering important questions about both adaptive and maladaptive development, as well as the critical importance of aspects of the environment, including social adversity and opportunities, for functioning.

Advances in human genetics research now allows for the computation of polygenic scores as measures of genetic influences for any individual with genotyped data. The ABCD Study genetics data includes youth genotypes that have now been used in the computation of numerous polygenic scores for a range of phenotypes. However, although phenotypic analyses clearly demonstrate links between family, experiential, and psychosocial factors and relevant brain and behavioral measures, including alcohol expectancies and subcortical volume and cortical thickness/area, thus far, there is relatively little evidence of incremental value in including polygenic scores in models (Gorelik et al., this issue; Johnson et al., this issue; Pine et al., this issue). Although in some respects, these null findings for polygenic scores are disappointing, they are nonetheless important for the field, as they indicate that even polygenic scores derived in GWASs of tens and hundreds of thousands, and in some cases, millions, of individuals and included in theory-driven models in a large sample of >11,000 youth, may not adequately capture the full genetic variance in relevant brain and behavioral phenotypes in early adolescence. These papers highlight the importance of continued work to further refine polygenic score approaches, especially considering age and developmental factors that have rarely been a concern for large scale GWAS, so that we can better measure and understand the role of human genetic variation during development.

Of particular relevance for polygenic score approaches is that GWAS has thus far been conducted primarily in samples of European ancestry, which functionally means that the derivation of polygenic scores has also been primarily conducted in European ancestry samples (Duncan et al. 2019). The predictive accuracy of polygenic scores derived among individuals of European ancestry is lower when then computed in non-European ancestry samples (Martin et al. 2019). This is of relevance for the ABCD Study, given that the sample reflects the racial and ethnic diversity of the United States, and, thus, includes a sizable minority of youth of non-European ancestry. Fortunately, recent, advanced methods, such as those described in Ahern et al. (this issue), offer new approaches to deriving polygenic scores in individuals of diverse ancestry that hold considerable promise for research in the racially/ethnically diverse ABCD Study sample and for other samples of non-European ancestry, thereby improving our science and promoting more equitable research efforts. Also of relevance is the upcoming Special Issue in *Behavior Genetics* on Inclusion, Diversity, Equity, and Access (IDEA), which will address these and other important issues for behavioral and quantitative genetics research.

Conclusion

The ABCD Study is a highly unique resource for researchers investigating a range of questions related to adolescent brain, physical, social, and mental health. Already highly impactful because of its relatively dense, prospective, longitudinal assessments of comprehensive measures of brain and behavioral functioning across the sensitive 10-year adolescent period, the ABCD Study will continue to gain in importance and value in the coming years, with the release of data from additional follow-up assessments. The genetically informative ABCD Study data allows researchers to address fundamental questions about human development and individual and contextual contributors to adolescent adjustment that simply cannot be answered using non-genetically informative study designs. By answering critical questions about adolescent brain and behavior, and identifying causal influences on adaptive and maladaptive development in the context of the social and environmental challenges facing today's adolescents, researchers using the ABCD Study genetic, family, and twin data will contribute to research informing targeted preventive-intervention efforts that most effectively promote adaptive outcomes for adolescents.

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