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The conception of the ABCD study: From substance use to a broad NIH collaboration

Nora D. Volkow[a], George F. Koob[b], Robert T. Croyle[c], Diana W. Bianchi[d], Joshua A. Gordon[e], Walter J. Koroshetz[f], Eliseo J. Pérez-Stable[g], William T. Riley[h], Michele H. Bloch[c], Kevin Conway[a], Bethany G. Deeds[a], Gayathri J. Dowling[a,*], Steven Grant[a], Katia D. Howlett[a], John A. Matochik[b], Glen D. Morgan[c], Margaret M. Murray[b], Antonio Noronha[b], Catherine Y. Spong[d], Eric M. Wargo[a], Kenneth R. Warren[b], Susan R.B. Weiss[a]

[a] National Institute on Drug Abuse (NIDA), National Institutes of Health, Bethesda, MD, USA
[b] National Institute on Alcohol Abuse and Alcoholism (NIAAA), National Institutes of Health, Bethesda, MD, USA
[c] National Cancer Institute (NCI), National Institutes of Health, Rockville, MD, USA
[d] Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Institutes of Health, Bethesda, MD, USA
[e] National Institute of Mental Health, National Institutes of Health, Bethesda, MD, USA
[f] National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA
[g] National Institute on Minority Health and Health Disparities, National Institutes of Health, Bethesda, MD, USA
[h] National Institutes of Health Office of Behavioral and Social Sciences Research, Bethesda, MD, USA

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ABSTRACT

Adolescence is a time of dramatic changes in brain structure and function, and the adolescent brain is highly susceptible to being altered by experiences like substance use. However, there is much we have yet to learn about how these experiences influence brain development, how they promote or interfere with later health outcomes, or even what healthy brain development looks like. A large longitudinal study beginning in early adolescence could help us understand the normal variability in adolescent brain and cognitive development and tease apart the many factors that influence it. Recent advances in neuroimaging, informatics, and genetics technologies have made it feasible to conduct a study of sufficient size and scope to answer many outstanding questions. At the same time, several Institutes across the NIH recognized the value of collaborating in such a project because of its ability to address the role of biological, environmental, and behavioral factors like gender, pubertal hormones, sports participation, and social/economic disparities on brain development as well as their association with the emergence and progression of substance use and mental illness including suicide risk. Thus, the Adolescent Brain Cognitive Development study was created to answer the most pressing public health questions of our day.

1. Introduction

Adolescence is a time of dramatic changes in brain structure and function. The malleability of the adolescent brain explains why this period is such a crucial time of growth: Young people are testing limits, enjoying novel experiences and social interactions, and becoming independent. At the same time, the specific ways in which the teenage brain remains immature, particularly the less developed circuits of the prefrontal cortex relative to other brain areas, contribute to the propensity of adolescents to engage in impulsive behaviors and to take risks (Somerville et al., 2010). This is crucial for healthy development; but inevitably, for many teens, it also includes a variety of unsafe behaviors like experimenting with addictive substances including tobacco, alcohol, marijuana, and other drugs. The fact that key brain areas have not sufficiently matured may make the teen brain more susceptible to being altered by those substances in both the short- and long-term, maybe even permanently.

Although advances in neuroimaging have revealed much about the impact of substances on the brain, many questions remain concerning how substance use and other experiences during adolescence influence brain development, and how they promote or interfere with later health outcomes such as addiction and mental illnesses. To what extent do

* Corresponding author at: 6001 Executive Blvd, Room 5103, MSC 9581, Bethesda, MD 20892-9591, USA.
E-mail address: dowlingg@nida.nih.gov (G.J. Dowling).

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tobacco, alcohol, marijuana and other drug exposures alter neurodevelopmental trajectories; and how does that, in turn, affect academic achievement, social and emotional development, and other aspects of life? Conversely, to what extent do different neurodevelopmental trajectories put children at greater risk for substance use? How do different types of substance use interact, and can the effects of individual drugs be disentangled in individuals who use more than one? Are the impacts of substance exposures persistent, or do they reverse when someone stops using them? To find answers to these questions, we must also understand something more basic: What is the normal trajectory of healthy human neurodevelopment—and is there even a single trajectory?

To comprehensively study the impacts of substance use and other experiences on adolescent brain development and health will require following a large cohort of children from early adolescence through the period of greatest risk for substance use, using neuroimaging and other sophisticated tools. Now is an opportune moment to embark on such a study, for three reasons. First, the rapidly shifting landscape of substance use in the United States has raised an unprecedented number of questions in many people's minds, particularly about the effects of marijuana, tobacco, and extreme binge drinking on young people. Second, the technical capacity to address the complex interactions of various environmental exposures and development (e.g., through non-invasive brain imaging, genetic analyses, and deep phenotypic characterization of individuals) now exists and can be deployed reliably and consistently at multiple sites across the country. And third, the ability to marshal common interest and funding across NIH institutes, necessary to support and guide a study of the needed scope, now exists, in part because of the Collaborative Research on Addiction at NIH (CRAN), a partnership formed in 2014 to leverage resources and expertise to promote research and training on polysubstance use and use disorders.

2. The shifting substance use landscape

Policymakers, parents, educators, and researchers increasingly want to know what the implications of adolescent substance use are for the developing brain, including how it affects life outcomes such as academic success and career achievement, as well as long-term mental and physical health. For instance, marijuana use by adults is increasingly accepted in our society, and as of this writing, most Americans live in a state where it is either legal for adult recreational use or available for medical use (National Conference of State Legislatures, 2017). At the same time, new synthetic drugs including cannabinoids (e.g., "Spice" products), cathinones ("bath salts"), and opioids (U-47700, W-18) have been emerging, often faster than authorities can monitor and control them. Novel ways of taking drugs (e.g., dabbing and edibles for marijuana) and new technologies such as electronic nicotine delivery systems (ENDS) are rapidly transforming how youth and adults use drugs, and raise different questions about how multiple substances interact to affect brain development. In addition, while the percentage of adolescents and young adults consuming alcohol has decreased, emergency department visits and hospitalizations related to excessive drinking have increased (National Institute on Alcohol Abuse and Alcoholism, 2013, 2014). No one yet knows how these changes might impact adolescents.

When CRAN was formed in 2014, the Directors of the three partnering Institutes (the National Institute on Drug Abuse [NIDA], National Institute on Alcohol Abuse and Alcoholism [NIAAA], and the National Cancer Institute [NCI]), quickly realized that a large longitudinal study was the most important contribution they could make together to answer fundamental questions concerning the impact of substance use on adolescent development. The ABCD Study will create a well-characterized nationwide cohort of 10,000 children starting at age 9 or 10 years and follow them through the subsequent decade. By analyzing brain development during the pre-exposure and exposure years, researchers will be in a position to clarify causal relationships between substance use and multiple associated outcomes. The study also aims to identify social and genetic vulnerabilities that may precede substance use as well as protective factors that might mitigate risk.

Dissociating the effects of different substances, which are typically not used in isolation (especially by adolescents), has been a limitation of prior research with insufficient sample sizes. The large cohort to be recruited for the ABCD Study will enable sufficient power to capture and analyze different patterns of substance use along with many other variables of interest. The study will also be able to tell us about differences between early initiation (early teens) and later or no initiation; heavy vs. occasional use; and interactions between drugs, alcohol, and tobacco. Such a large sample, which includes 800 pairs of twins, will also allow researchers to tease out the effects of other variables such as genetics, socioeconomic status, social support systems, and other biological and behavioral factors associated with substance use, brain development, and other outcomes.

3. Technological advances

Over the past 10 years, developments in non-invasive neuroimaging, most notably in functional magnetic resonance imaging (fMRI), have increased our ability to safely study the developing brain and to harmonize data across multiple platforms. Large-scale projects such as the Human Connectome Project (HCP), designed to map the neural pathways that underlie human brain function, have established standards for conducting large-scale neuroimaging projects. The HCP developed a set of broadly useful, thoroughly tested, MRI acquisition protocols, image reconstruction algorithms, and numerous publicly available neuroimaging software and informatics tools that have informed ABCD's neuroimaging protocol development (Van Essen et al., 2012).

Similarly, recent collaborative projects have demonstrated the feasibility of conducting multi-site neuroimaging studies in children, laying the foundation for a much larger, comprehensive study of adolescent brain and cognitive development. Such projects include the Pediatric Imaging Neurocognition Genetics (PING) study—a cross-sectional brain imaging (MRI) and genetics database of more than 1500 children and adolescents, designed to map the genomic landscape of the developing brain (Jernigan et al., 2016)—and the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA)—a brain imaging (MRI) study of adolescents designed to determine both the effects of alcohol exposure on brain development and to identify pre-existing vulnerabilities for an alcohol use disorder. The NCANDA study recruited more than 800 youth between the ages of 12 and 21 for imaging and neuropsychological testing in an accelerated longitudinal design (Brown et al., 2015), establishing the feasibility of a large-scale prospective study in terms of both recruiting large numbers of suitable participants and harmonizing imaging data from different platforms.

Recent advances in data analytics and data sharing also make a study like ABCD only now possible: Decreasing costs of genotyping have made it feasible to perform genetic analyses in large cohorts; technological capacity can now provide temporally dense data on behaviors and their contexts; and access to computational infrastructure and analytics has made it possible to collect and analyze large data sets. Advances in data storage and transfer capacity and informatics are enabling researchers across the country (and world) to share and analyze anonymized data.

NIH has been promoting data sharing for more than a decade, but concerns about replicability due to small sample sizes have shifted the scientific culture toward greater acceptance of data sharing as a routine part of doing science. We are now seeing an increased pace of scientific discovery as a result. The HCP, for example, has produced more than 160 papers in a very short span of time (2012-present), thanks to broad sharing of data as well as new tools and resources for data analysis.

Table 1
Potential Implications of ABCD Study for Policy and Practice.

Questions the ABCD Study Could Answer:	Implications for Policy/Practice:
Are there differences in marijuana use/consequences between youth from states where it is illegal and those where it is legal for adult recreational use or for medical use?	Marijuana laws/regulations
How does use of e-cigarettes influence youth uptake and use of other tobacco products as well as alcohol and other drugs?	E-cigarette laws/regulations
Are there biomarkers or other signs of premorbid mental illness?	Early interventions to prevent the transition to mental illness
Do certain extracurricular activities (e.g., sports, music) lead to better health and educational outcomes?	After-school programming
How does the use of different forms of digital media and/or amount of screen time exposure impact brain, social, and cognitive development?	Advice and guidance for parents, teachers, and digital media developers
How prevalent are traumatic brain injuries among student athletes and do they influence brain development and educational achievement?	Precautions, assessments, and education of student athletes
What is the impact of different sleep patterns on brain development and academic outcomes?	School start times

4. Broad interest across multiple NIH institutes

Substance use does not exist in a vacuum; it is entwined with mental and physical health and with our social systems in myriad complex ways, as is neurodevelopment. Thus, even as the ABCD study was being conceived, the CRAN Institute Directors realized that it would have to address a wide range of questions about genetic influences and environmental exposures on neurodevelopment during the second decade of life. Other Institutes, Centers, and Offices across the NIH similarly recognized the value of the proposed cohort for addressing pressing questions in their own priority areas. Answers to these questions could inform policies and practices to improve public health in a variety of ways (see Table 1 below).

The National Institute of Mental Health (NIMH) was an obvious collaborator in the study, since mental disorders often begin in childhood or adolescence and frequently co-occur with substance use (Kessler, 2004). One of NIMH's strategic research priorities is to chart mental illness trajectories to determine when, where, and how to intervene. The ABCD study provides a unique opportunity to delineate the association between brain development and the emergence and progression of psychopathology so that premorbid signs of illness and sensitive periods for intervention can be identified. The study will provide much-needed information on low-incidence behaviors (e.g., suicide attempts) that cannot be garnered from smaller studies and will be able to address critical, lingering questions about the bidirectional influences of substance use and psychopathology, such as the complex interrelationships among marijuana use, schizophrenia, and genetic vulnerabilities. By filling these existing gaps in knowledge, the ABCD study will provide a foundation for altering trajectories of risk and improving the lives of those with substance use or mental disorders. The NIMH also brings to the project its expertise in developing large-scale imaging databases suitable for widespread sharing (e.g., the HCP database).

Another valuable collaborator to ABCD, the NIH Office of Behavioral and Social Science Research (OBSSR), brings to the study a crucial and timely focus on several environmental and behavioral factors that affect growth and development, including sleep patterns, physical activity, screen time, exposure to stressful events, and social support systems and networks. These are pressing questions for parents concerned with the health, including brain health, of their teenage children. Assessing these environmental and behavioral factors along with neurodevelopmental processes will improve our understanding of how these various experiences shape brain function and development. Importantly, the ABCD study will also be able to evaluate how well self-reported measures of substance use and risk-taking attitudes correlate with imaging and biological measures over time, a significant contribution to the field of behavioral science.

With the growing racial and ethnic diversity of the U.S. population, about half the sample in the ABCD Study will be from minority groups. The National Institute on Minority Health and Health Disparities (NIMHD) brings to the ABCD study a crucial focus on the ways socioeconomic, cultural, racial, and ethnic variables both affect and may be affected by substance use, mental health, and other life and health outcomes. Substance use behavior varies by race and ethnicity as well as by socioeconomic status and gender—for example, tobacco use among most minority youth is less prevalent than among Whites (Johnston et al., 2017), even though some minorities have worse socioeconomic status and higher levels of daily stress from discrimination, food insecurity, and diminished educational opportunities. By assembling a cohort that reflects the diversity of the U.S. in terms of race, ethnicity, gender, urbanicity, and socioeconomic status (for detailed information on sampling methodology, see Garavan et al., in submission), the ABCD study will provide an opportunity to evaluate the extent to which these differences and similarities are related to neurodevelopment and other aspects of adolescent health.

The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and the National Institute of Neurological Disorders and Stroke (NINDS) were also natural partners in the project because of their interest in healthy brain development, the interactions between environmental factors and brain development, and the effects of childhood sports. There is much we do not know about the impact of contact sports and non-contact sports on brain function, particularly for this age group. On one hand, the physical activity and social interactions provided by youth sports can be strong positive influences on physical and mental health; however, an estimated 630,000 U.S. emergency department visits annually are accounted for by children who present with symptoms of traumatic brain injury (Faul et al., 2010), and up to 13% of them continue to experience physical and/or cognitive symptoms more than 3 months after the injury (Barlow et al., 2010). Increasing societal awareness of the risk for traumatic brain injury during organized sports has made this a specific and pressing question, not only for researchers but also for parents, educators, and coaches. In addition to giving information about the prevalence and impacts of traumatic brain injury in youth, the ABCD study will be able to provide information on how such injuries affect substance use risk and, in turn, how substance use affects risk for traumatic brain injury.

ABCD's longitudinal design also offers an extraordinary opportunity to evaluate multiple biological and environmental influences on typically developing children's neurocognitive and brain function. For example, by measuring pubertal hormones over time, the ABCD Study will allow us to assess how hormones affect brain structure and function, and behavior during adolescent development. Without a baseline to delineate typical brain development, it is difficult to diagnose traumatic brain injury or other potential neurodevelopmental problems if a child visits the pediatrician with symptoms. One of the most important contributions of ABCD is that it will provide, for the first time, benchmarks of healthy brain development—akin to growth curves for height

and weight—across the second decade. Pediatricians, psychiatrists, neurologists, and school counselors may be able to use these benchmarks to identify potential problems and risks—for depression or Attention Deficit Hyperactivity Disorder (ADHD), for example, as well as substance use—and thus facilitate early intervention. These benchmarks will also help researchers identify protective factors that promote resilience and healthy development in the setting of potential risks or other disadvantages.

5. Engaging the scientific community in developing the ABCD framework

While it was clear that a large-scale study of adolescent brain and cognitive development was needed to answer these broad yet interrelated questions, a clearly defined scientific framework was still needed to guide the development of the Funding Opportunity Announcements (FOAs). In May 2014, NIDA, NIAAA, NCI, NICHD, and NIMH convened an expert panel workshop meeting summary at https://addictionresearch.nih.gov/summary-expert-panel-meeting to develop recommendations for the best large-scale research designs and measures to assess the developmental effects of substance exposure. The expert panel discussed key research questions such a study should answer, as well as critical design elements from sampling size and strategy to imaging, cognitive, and other behavioral measures. There was general agreement that the study should be large and longitudinal, recruiting participants prior to substance use initiation (e.g., beginning at ~ages 10–12) and following the cohort throughout the period of greatest risk (~ages 19–21). Importantly, the meeting focused on how the ABCD Study could go beyond what other smaller studies had achieved, to serve as a platform for scientific discovery and a foundation for parallel mechanistic studies in animal models.

Following the workshop, the NIH released a formal Request for Information (RFI) at https://grants.nih.gov/grants/guide/notice-files/NOT-DA-14-014.html and held a satellite symposium meeting summary at https://addictionresearch.nih.gov/sfn-meeting-summary the annual Society for Neuroscience meeting in Washington, D.C. to obtain broader input from extramural researchers and other public stakeholders on all aspects of the study—including optimal sample size and sampling strategies; approaches for replication of findings; the most appropriate neurocognitive, behavioral, and neuroimaging measures; methods for biospecimen collection and analyses; and arrangements for data sharing. While the scientific community was not in complete agreement on all of these areas, their input was vital to creating a framework for the development and release of the FOAs in January 2015. There was a robust response to these announcements in which applicants proposed study designs and specific measures that would address the research questions outlined in the FOAs within the overarching framework. Applications underwent NIH peer review during the summer and awards were made in September 2015.

6. Conclusion

The ABCD study is a collaborative trans-NIH venture, bringing together a wide range of scientific research agendas and expertise, to answer some of the most pressing public health questions of our day. The collaboration continues to expand, with involvement now of the NIH Office of Research on Women's Health, the Centers for Disease Control and Prevention-Division of Adolescent and School Health, and the National Institute of Justice. The study will yield important insights into mechanisms and causal relationships that have previously proved elusive, inform the development of new prevention and treatment strategies, and give rise to new research areas we cannot yet anticipate. The massive data resource ABCD will create will be utilized by the entire scientific community for decades to come; the study will release curated, anonymized data annually to the research community (along with the computational workflows used to produce the data), which will allow scientists from all over the world to conduct analyses, pool resources, and find the answers to unforeseen questions about adolescent brain development and factors that interact with it. And in addition to data about perturbed developmental trajectories, ABCD will also generate valuable benchmarks for normal structural and functional neurodevelopment during the transition from childhood into young adulthood, a lasting contribution to medicine. ABCD will thus inform not only mental health and substance use researchers but also educators, parents, physicians, and policymakers—everyone with a stake in the health of our nation's youth.

Conflict of Interest

None.

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