Developmental Cognitive Neuroscience 32 (2018) 161–164

Contents lists available at ScienceDirect

Developmental Cognitive Neuroscience

journal homepage: www.elsevier.com/locate/dcn

Commentary

# Implications of the ABCD study for developmental neuroscience

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A B S T R A C T

The Adolescent Brain Cognitive Development Study (ABCD) will capture a breadth of multi-faceted biobehavioral, environmental, familial, and genetic longitudinal developmental open-access data from over 11,000 9–10 year olds throughout the United States of America (USA) for an envisioned ten-year span. This will subsequently represent the largest study ever attempted with this level of brain phenotypic detail. This study holds the opportunity for exciting advances in the understanding of typical adolescent neurodevelopment, discovery of neurodevelopmental underpinnings of mental illness, as well as the neurodevelopmental influences of (and on) social factors, substance use, and critically – their interaction. This project will certainly take unprecedented steps in informing the nature of adolescence and the developing brain. The scale and open-access features of ABCD also necessarily entail areas for consideration to enhance the integrity of the ABCD study, and protect against potential misuse and misinterpretation of ABCD data. Ultimately, with the open-source data, all scientists in the broader community have as much responsibility as the investigators within the Consortium to treat these data with care. It will be fascinating to see what dynamic data these paths generate. ABCD is poised to exemplify how large-scale longitudinal developmental neuroscientific studies can be designed and efficiently conducted.

## 1. Overview of the special issue

This Special Issue features articles describing the historical and methodological details of the Adolescent Brain Cognitive Development Study (ABCD). ABCD will follow an epidemiologically-informed cohort of pre-adolescents and their families into adulthood with repeated assessments of neural structure and function as well as measures of behavior and mental health. As discussed in this Issue by Jernigan et al., 2018, along with Volkow, Koob and colleagues (Volkow et al., 2017), one of the most fundamental and impactful aspects of ABCD includes the breadth of multi-faceted biobehavioral, familial, and genetic longitudinal developmental data being collected within this essential developmental window; a window that has historically been overlooked within the developmental health and science literatures (Bundy et al., 2018). Indeed, while definitions of adolescence continue to evolve (Giedd, 2018), by August 2018, an enormous and carefully-considered array of brief, but in-depth psychometrics will have been collected on > 11,000 9–10 year olds, including an embedded twin cohort, throughout the United States of America (USA). This will likely represent the largest study ever attempted with this level of brain phenotypic detail, articulated to capture the nature of neurodevelopment as children (many of whom will be pre-pubertal at the time of initial enrollment) enter adolescence (e.g., transition into puberty), and through the 10 year stretch of this enigmatic developmental period. Building on essential foundational studies (Blakemore and Choudhury, 2006; Casey et al., 2000; Giedd et al., 1999; Sowell et al., 2003), as discussed within this Special Issue, data from ABCD will address critical questions about the nature of adolescence, including how the brain develops throughout this period, how integral dimensions of mental health (Barch et al., 2017), interacts with structural and functional metrics of cognitive development (Casey et al., 2018), neurocognition (Luciana et al., 2018), biological functioning (Uban et al., 2018), culture and environment (Zucker et al., 2018), substance use (Lisdahl et al., 2018), and gene by environment (G × E) interplay within these relationships (Iacono et al., 2017). Epidemiological sampling strategies have promoted a socio-demographically-balanced (rather than convenience) sample. As delineated within this Issue, the ABCD sample has been further enriched with participants more likely to transition into risk behaviors (Loeber et al., 2018), which is hoped to generate sufficient numbers of distinct brain trajectories to power critical individual-difference analyses.

The recruitment plan, assessment batteries, and family engagement

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[1] Funding for this manuscript was supported by: U01DA041120 (for Bjork and Luciana) and 1U01DA041148 (for Feldstein Ewing).
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https://doi.org/10.1016/j.dcn.2018.05.003

of ABCD have benefitted from an enormous degree of oversight and engagement from a variety of stakeholders. This level of oversight and feedback, which have occurred at all stages of this project thus far, are aimed to help the Consortium anticipate and address the complex interplay of factors inherent within an enormous, high-profile project engaging children and their families over a full decade. To that end, as captured within this Special Issue, this study has been carefully and systematically designed to ensure time-efficient, harmonized, and high-quality data collection as managed by: the Consortium's Coordinating Committee and assessment oversight teams (Auchter et al., 2018), an overall Design workgroup (Garavan et al., 2018), and a Data Imaging Acquisition and Management team (Casey et al., 2018). Also detailed within this Issue include planned retention strategies, which will nimbly evolve using in response to emergent technologies (Feldstein Ewing et al., 2017a,b), plans for staying connected with youth via mobile technology/social media platforms (Bagot et al., 2018). Finally, this Issue details how additional levels of accountability have been leveraged (Barch et al., 2017), via national and international experts outside of the Consortium (Charness, 2017) and community stakeholders (Hoffman et al., 2018) to maximize input at all levels of the project.

## 2. Avenues for opportunity

Decades of cohort studies have provided exquisite longitudinal data on the effects of genes and early environmental exposures in shaping adolescent behavior and mental health and later psychosocial outcomes during adulthood (Brown et al., 2015; Dick et al., 2016; Rueben et al., 2016). What is novel about ABCD is its potential (via cutting-edge neuroimaging) to enable the field to discover the neurodevelopmental architecture that underpins these influences, as well as temporal relationships between variables that may contribute to an array of neurodevelopmental trajectories.

If prior large-scale multi-site examinations in addiction and neurodevelopment (e.g., Project MATCH; PING; HCP; NCANDA; IMAGEN) are accurate predictors, the enormous scale and epidemiological-driven population-based sampling of ABCD will facilitate the ability to apply neurodevelopmental theories to individuals from varied racial/ethnic, economic, educational, and geographically diverse backgrounds. These and other novel explorations are only beginning to be realized with the first wave of open data release. Examples from the Consortium suggest that this immense undertaking may include catalyzing the generation of highly sophisticated imaging (MRI) measurement approaches across sites and scanners, that will, at a minimum, improve resolution and prediction of routes of typical and atypical development. This would include potential early-stage brain markers that could better alert and guide medical and psychological practitioners in the detection of deviations from healthy growth and development. Similarly, the intentional recruitment across a socioeconomic spectrum holds potential to detect not only routes for adversity, but also how youth may withstand and flourish despite adversity, and excitingly, the neurocircuit underpinnings of that resilience. Of great interest to many in the Consortium is how these data will feed forward into the growth and development of risk factors around substance use exploration, initiation, and progression; including both routes into more serious use, as well as facilitated and pathways out of substance use en route to adulthood (Cousijn et al., 2018).

## 3. The integral contribution of this study to our models of adolescent substance use

A particular motivation in the conceptualization of ABCD and its support from NIH stakeholders lies in its ability to inform our understanding of substance misuse and its impacts on the developing brain. Epidemiological surveys, such as Monitoring the Future (Johnston et al., 2018) and the United States National Survey on Drug Use and Health (NSDUH) (Substance Abuse and Mental Health Services Administration, 2014), have allowed researchers and clinicians to appreciate the significance of associations between an early onset of substance use and the later development of substance use disorder. What remains unclear is why misuse of commonly-used substances such as alcohol, cannabis, and nicotine during adolescence represents a potential vulnerability factor. One explanation is that substance use introduces a form of neurotoxicity during a sensitive developmental period, which subsequently alters neural circuitry and its functioning in an enduring manner into adulthood (Guerri and Pascual, 2010; Jacobus and Tapert, 2013). Alternatively, because adolescence is characterized by peer salience, identity development, and the individual's selection of his/her niche in the world at large (Schriber and Guyer, 2016), sociocultural factors coincident with substance misuse can interact, disrupting and interfering with healthy growth trajectories (c.f., Cruz et al., 2012). Genetically-informed studies suggest that premorbid individual variations in externalizing and internalizing traits impact patterns of substance use onset (King et al., 2004), and indeed, individual difference factors may be generally overlooked in current appraisals of adolescent risk behaviors (Bjork and Pardini, 2015). Thus, there is likely a complex pattern of interactions among individual difference factors, genetic variations, cultural context, and substance-related neurotoxicity that impacts long-range outcomes. The reliance to date on small sample studies within narrow geographic bands has been prohibitive to our understanding of how these sources of variation interact over time. Thus, ABCD offers, for the first time, a careful avenue to disaggregate the nature of these interactive forces, in order to more fully inform the nature of adolescent substance use and its impact on the developing brain.

Another advantage of ABCD for understanding the neurobiology of adolescent substance misuse is the inclusion of high-risk samples. To fully appreciate the impact of substance use on developmental trajectories, those trajectories are best examined when compared with typical development. Here, the developmental addiction neuroscience field has been historically been limited, given that best understandings of what is typical relies largely on high-functioning convenience samples or on small case-control comparisons in the psychiatric literature. Other significant limitations have historically included high rates of comorbidity in youth who experiment and misuse substances, and inability to capture premorbid characteristics prior to substance use onset. As discussed in this Issue, because the baseline ABCD sample is largely substance-naïve (Lisdahl et al., 2018), ABCD brings an unprecedented opportunity to evaluate predictors of use onset across the full U.S. population as well as how these factors influence adult outcomes.

Of relevance to the readership of *Developmental Cognitive Neuroscience*, the ABCD study also provides a unique opportunity to understand the nuances of typical development, particularly in light of inclusion of multiple imaging modalities; this approach will necessarily facilitate the capacity to address critical questions around the brain's structural integrity, structural connectivity, functional responses in the context of working memory, inhibitory control, and reward anticipation, as well as the brain's functional connectivity at rest. Alignment of the protocol with other large-scale efforts (e.g., the Human Connectome Project) assures synchronicity and relevance of the selected methodologies. Moreover, behavioral development will be reliably tracked using standardized and well-validated assessments, such as cognitive tests from the NIH Toolbox$^{R}$ and metrics from NIH's PhenX behavioral batteries.

Particularly exciting is the opportunity to test theories that have focused on pubertal development as a trigger for subsequent increases in sensation-seeking and later risk-taking (Byrne et al., 2017; Nelson and Guyer, 2011). Given that thousands of children within the ABCD baseline cohort are pre-pubertal, the inter-twining of behavioral and neural variables in the context of advancing puberty (Boivin et al., 2018) and informed by hormonal assessments will be available for examination across numerous factors including race/ethnicity, gender,

socioeconomic status, and child and parent level of education. Additionally, increasing community and scientific attention has been focused on the intersection of adolescent behavioral and neurocognitive health risk and changes in youth sleep; these questions, including timing of these relationships will be able to be examined through these data (Drollette et al., 2014; Robinson et al., 2018). ABCD's inclusion of comprehensive measures of culture and environment will allow new and exciting advances in the field of cultural neuroscience (Han et al., 2013). Simply put, it is unknown whether the field's current models of neurodevelopment (Ernst et al., 2011; Harden et al., 2017; Smith et al., 2015) are salient for individuals across a diversity of backgrounds and experiences. Isolation of invariant versus variant developmental patterns would be a major advance for the field. We hope that these few examples engender as much enthusiasm about the potential impact of ABCD on developmental cognitive neuroscience as we are experiencing as investigators within this Consortium.

Although the ABCD is an observational "natural history" study, and not an interventional study, ABCD data will nevertheless have the capacity to inform contemporary conversations and public health policy, by allowing data-driven responses to ongoing questions such as gender differences in the developing brain (are boys different than girls?), the impact of sports on the developing brain (e.g., football, soccer), the connection of electronics use to academic performance and other developmental cognitive metrics. Other highly salient public health issues that can be addressed through this study will, by default, include how large unexpected crises impact developing cognitive functioning and health during the time of testing. For example, U.S.-based Hurricanes Irma and Maria took place during the course of the study, enabling exploration of how youth tested at our Florida International University site may compare both before and after disaster struck, but also cross-sectionally post-disaster across numerous constructs with their same age peers in non-affected regions.

One key controversial public policy issue concerns cannabis regulation in the U.S., and the potential effects of expanding cannabis decriminalization on the developing adolescent brain. At ABCD's commencement, two sites were located in regions with recreationally-legal cannabis (Colorado; Oregon), with a third site (California) adopting decriminalization of recreational use during project enrollment. Other U.S. public health emergencies around opioid use have also unexpectedly come into play during the course of this project (Dash et al., 2018). Due to forthcoming releases of the data in a well-annotated and pre-processed format, individuals within and outside of the Consortium who routinely analyze cognitive or psychometric data, or those who do not have extensive technical expertise with neuroimaging will be able to disentangle the relationships between these public health questions and adolescent health and neurodevelopment, in a manner that has been difficult to achieve outside of the framework of the Consortium (e.g., Feldstein Ewing et al., 2017a,b). This will be critical for state and national policymakers, who need precisely this type of data to inform decision making in education, prevention, and intervention/treatment programming.

## 4. Avenues for consideration within the ABCD study

The open-access model of ABCD reflects the emerging zeitgeist of transparency and reproducibility in science (Ioannidis and Khoury, 2018), and holds potential to "let a thousand flowers bloom" with discovery science. This poses its own set of problems, however. We note, for instance, that complications with the open-access model prompted a recent NIH initiative to foster responsible use of the data (RFA-DA-19-006). First, the ABCD dataset could potentially be used to reify or confirm pre-posed ideas, by hand-picking select elements. Few data modalities are more vulnerable to method variance than neuroimaging data, with its litany of preprocessing steps (pipelines), what may seem to be arbitrary thresholds of excessive motion and differing corrections (or not) for multiple comparisons. In our emerging era of "alternative facts" and growing distrust in institutions [including in science and scientists (Open Science Collaboration, 2015; Van Bavel et al., 2016)], there is high potential for analysts with ideological or economic agendas (e.g. to promote an industry, social policy, or to get a grant funded) to selectively choose participants, brain structures, and phenotypes to suggest (or disavow) a deleterious effect of an environmental factor or other individual difference. While this certainly can happen within investigators' own "proprietary" datasets, this potential is nevertheless greater with open access data, despite how the Consortium plans to release already-processed individual-level image data, including fMRI task activations. Journal editors and science writers will need to be vigilant for mis-use of data, potentially via routes such as offering opportunities for "rebuttal analyses".

In addition, the sheer size of the ABCD study holds potential for reports of "significant" individual differences of negligible magnitude. With today's rapid news-cycle that prioritizes sensationalism over context, we can envision a scenario where American parents confiscate smartphones from their crestfallen adolescents following publications, for example, that screen time accounts for 1% of the "shrinkage" in prefrontal cortex volumes of ABCD youth. This example is lighthearted, but is illustrative of the core of recent initiatives to report individual or group differences in terms of effect size (Sullivan and Feinn, 2012). Perhaps the advent of mass-scale neuroimaging papers will necessitate mandatory effect size metrics into developmental neuroimaging literature. Moreover, the compendium of different assessment modalities in ABCD will allow the potential correlation of "everything" with "everything else." While healthy skepticism in peer review may protect against publication of mechanistically-implausible associations, one potential solution to avoid reporting completely spurious associations would entail splitting the ABCD sample into discovery (model-fitting) and replication (model-testing "hold-out") samples, as suggested within RFA-DA-19-006.

Because there is no practical way to regulate which analysis teams around the globe interrogate which components of the ABCD dataset to ask which precise questions about adolescent brain development, there is a high likelihood that numerous similar analyses (especially low-hanging fruit) might be simultaneously submitted to the literature. With original data-acquisition methods essentially held equal across submissions, it will be incumbent upon journal editors and peer reviewers to discriminate article impact or significance based on the quality, innovation, and validity of the statistical and analytic techniques. Another unique twist of ABCD is the intersection of open access with a longitudinal design. One potential consideration is how the field may rate the merit of ABCD manuscripts over the next couple years, when more temporally-definitive samples (especially of smaller subgroups) or samples who show greater risk-taking will require waiting for more data in future assessment waves.

## 5. Conclusion

Clearly, the scientific potential of the open-access ABCD dataset outweighs these concerns, but when considering how this study will innovate the field of developmental neuroscience, these potential impacts merit consideration. With the open-source data, all scientists in the broader community have as much responsibility as the investigators within the consortium to treat these data with care. It will be fascinating to see what dynamic data these paths may generate; it is certain that they will all advance our knowledge and understanding of adolescent development

In conclusion, as investigators within the ABCD Consortium, we are awestruck by what has been achieved across data collection sites in a relatively brief period of time. We are gratified by the engagement of our parent and child participants and look forward to interacting with them for decades to come. ABCD is poised to establish a precedent world-wide for how longitudinal developmental neuroscientific studies can be designed and efficiently conducted.

## Conflict of Interest

None.

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