Editorial: Understanding the Child at Risk for Substance Use Disorders: Neuroimaging Addiction Risk

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Recent surveys demonstrate skyrocketing rates of adolescent vaping,[1] while the opioid epidemic, rightfully, is daily front page news. At the same time, the public perceives cannabis as a harmless source of recreation or even as cure-all therapy. Now more than ever, child and adolescent psychiatrists, politicians, policy leaders and parents need empirical support to bolster the position that drugs of abuse should be avoided by young people. We have a robust literature connecting cannabis use to earlier and worse psychotic disorders,[2] as well as strong longitudinal data implicating cannabis in various neuropsychological deficits.[3] What our field lacks, however, are brain imaging studies that definitively document the negative neurobiological impact of substance use on the developing human brain. The key to appreciating why this research literature is so limited has to do with one of the core tenets of substance use disorder (SUD) etiology: SUDs do not emerge *de novo* in adulthood or late adolescence when people typically present with impairing symptoms. Decades of research now suggests that certain latent childhood traits predispose some youth to initiate and then escalate drug and alcohol use more often than is typical.[4] Children born into families with SUDs are more likely to express these highly heritable traits and are additionally subject to environmental risk factors and adversity. Therefore, children born into families with SUDs are disproportionately laden with genetic and environmental factors that shape brain structure and function. In other words, prior to exposure to drugs of abuse (which themselves may influence the brain), some children's brains already differ from those of typically developing youth. This observation limits the usefulness of cross-sectional neuroimaging studies that compare youth who have used drugs to those who have not, because of the non-random interaction of latent traits, environmental factors, and pre-existing brain differences. This interaction likely accelerates these adolescents' propensity to initiate and continue to use drugs of abuse.

The study by Vaidya *et al*.[5] in this issue advances the SUD risk literature with their finding of lower functional connectivity between premotor and sensorimotor network nodes in youth with a family history of alcohol use disorders. Rather than focusing on brain structure or blood flow during brain activation, Vaidya *et al*., expand work in this area by examining intrinsic functional connectivity in 191 adolescents with and without a family history of alcohol use disorders. Intrinsic functional connectivity, also known simply as functional connectivity or resting state functional connectivity, is a relatively recent advance in magnetic resonance imaging.[6] It allows for the investigation of activation that is temporally correlated between regions and is thought to comprise long range functional networks. Interestingly, these networks appear active even when a person is resting and, in fact, the majority of the brain's energy appears to be dedicated to these functional networks which may keep the brain primed in an active and efficient state for future behaviors. Approximately 10 networks have been identified and associated with specific functions such as auditory, visual and executive control.[7] Rather than selecting which regions of the brain the research team would focus on in advance, as similar studies have done, Vaidya *et al*.[5] used a statistical technique, independent component analysis (ICA), that searches the whole brain for correlations between regions. This approach allowed for a data-driven, exploratory investigation of temporal correlations, free of the bias that using pre-identified regions introduces. This approach uncovered lower intra-network connectivity within a dorsal-premotor sensorimotor network in youth with families with alcoholism. While some may find it surprising that other networks were not different between the groups, the areas implicated were noted by authors to play a role in motor and cognitive processes, in particular mental processes that do not require overt movement. Of note, the authors also found functional

connectivity correlations with deficits in visuomotor planning, additional evidence of a motor-relevant risk profile for SUDs. These findings highlight the need for future work to further delineate specific sensori-motor/cognitive-motor deficits that may predispose to SUDs--certainly an understudied area of SUD risk.

In addition to tackling the issue of connectivity influenced by a family history of alcoholism, the investigators made fundamental contributions to the literature on age related differences in functional connectivity. Previous research has found that connections between subcortical and cortical areas decrease with age, while connections among cortical areas tend to increase.[8] It has also been reported that over time, functional networks develop from local networks in childhood to longer, range more distributed networks in aduldtood.[9] Vaidya *et al*.[5] did not find connectivity interactions between age and family history of alcohol use disorders, but they did report on a number of age-related findings that suggest that the strength of the correlations between various brain regions changes fairly dramatically across just a few years of adolescence. First, older youth between 17-18 years, showed greater connectivity between the majority of networks than younger participants. For example, in the older adolescents, the auditory network had stronger connectivity to various networks including executive, frontal, sensorimotor, and visual. Conversely, the 13-14-year-old group had stronger connectivity only between cerebellar components and other brain regions, although cerebellar-frontal connectivity was greater in older youth, suggesting that the cerebellum shifts focus from sensorimotor to higher order cognitive functioning as adolescents mature. These findings are consistent with another recent examination of cerebellar development.[10]

Returning to the initial controversy raised in this editorial: In the absence of a large sample of longitudinally imaged youth who use drugs of abuse and are compared to appropriately matched comparison subjects, how do studies like Vaidya and colleagues[5] advance us toward the goal of understanding the developmental effects of various drugs of abuse? First, these cross-sectional high-risk neuroimaging studies highlight potential targets for preventive interventions that otherwise might not be known from behavioral studies. Second, more broadly, they illustrate the need for longitudinal studies by quantifying the heterogeneity in brain function and structure prior to drugs of abuse. Longitudinal studies are costly and difficult to conduct, but methodologically superior to cross-sectional studies to address developmental questions. This literature will undoubtedly accelerate as the early findings of the Adolescent Brain Cognitive Development (ABCD) Study are published. The ABCD study represents an unprecedented National Institutes of Health (NIH) investment into the phenotypic and neurobiological characterization of nearly 12,000 youth. These youth have been recruited are being followed through adolescence and adulthood so that the Holy Grail of addiction research questions (along with a plethora of others) can be answered: What do drugs of abuse do to the brain? The ABCD and other studies will likely provide those answers in the future. As we await these studies, neuroimaging high risk, but drug and alcohol naïve youth such as those in the focus of this editorial represent an ongoing area of research that points to substantial differences in brain structure and function in youth at elevated risk for SUDs. Vaidya *et al*.'s work points to novel targets for future prevention and intervention research: sensorimotor deficits within functionally connected networks.

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