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Commentary: Substance Use and the Brain: It's Not Straightforward to Differentiate Cause From Consequence – A Commentary on Kim-Spoon et al. (2020)

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Abstract

That substance abuse is associated with differences in brain structure and function and related neurocognitive impairment is undisputed. Causally informative study designs, such as the prospective, longitudinal study leveraged by Kim-Spoon et al. (2020), as well as twin and family studies, are necessary for answering vexing but critical questions about substance use and the developing brain. Investigations that seek to differentiate cause from consequence and identify the factors that initiate the cycle of addiction have the potential to transform our understanding of the development of substance use and abuse, prompt revisions to current models of addiction, guide the most strategic preventive-intervention efforts, and ultimately improve the lives of millions of affected individuals and their families.

That substance abuse is associated with differences in brain structure and functioning and related neurocognitive impairment is undisputed. Most models of addiction implicitly or explicitly attribute these differences to neurotoxic exposure effects of substances on the brain and related functioning. Substance use and abuse is associated with differences in the brain circuitry underlying cognitive control, reward, emotionality, and learning/memory processes. The brain disease model of addiction (Volkow, Koob, & McClellan, 2016) delineates effects of substances on interrelated systems: desensitization of reward-related processing, increased stress that reduces cravings, negative emotions when cravings are unsated, weakening of cognitive control abilities that leads to repeated relapse, and changes to learning/memory processes with long-term use. However, the vast majority of the existing substance use research has relied on cross-sectional studies with heavy, chronic substance using adults. As such, it is not possible to differentiate the consequences of substance exposure from pre-existing dysfunction that confers causal risk for substance initiation and use. Experimental animal studies clearly implicate exposure-related effects but cannot speak to why humans first start using substances or why some use in a more problematic way than others—the factors that initiate the cycle of addiction in the first place. And once substance use is initiated, it is also often difficult to distinguish the direct molecular effects of

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substances on the brain from effects on the brain of the various learning, habit, affective, and behavioral changes associated with addiction.

Adolescence and the transition into emerging adulthood, a period during which substance initiation and use is to a degree normative, and during which problematic use and rates of substance use disorders increase rapidly (Substance Abuse and Mental Health Services Administration, 2019), is an optimal time for investigations of normative developmental and individual difference factors that underlie general risk toward substance use and abuse, or increased risk for particularly vulnerable individuals. Dual-systems models of adolescent decision-making and risk-taking highlight the imbalance in the respective maturation during adolescence and emerging adulthood of the brain regions underlying bottom-up reward-related processes and top-down control processes (Shulman et al., 2016). Heightened reward sensitivity and incentive motivation may bias adolescents to seek out rewarding, novel, and sensation-enhancing stimuli (including substances) while as yet less well-developed and inefficient cognitive and related inhibitory control abilities may make resisting such reward-seeking behaviors difficult. Thus, the developmentally normative but relative immaturity of the adolescent brain and consequent deficits in top-down control mechanisms may make it generally more difficult for adolescents to inhibit behaviors related to substance use. These processes occur in the context of (and may also give rise to) developmentally normative shifts during adolescence toward identification with the peer group and increasing susceptibility to social reward and peer influence. However, even beyond normative development, individual differences in the brain circuitry underlying control and reward processes also likely play a critical role for predisposing some adolescents toward substance initiation or the development of problematic use. That is, adolescents with a greater relative mismatch of control and reward processing abilities (due to deficits or relative delays in control processes and/or to greater reward sensitivity or relatively rapid development of reward processing) may be at greater risk. Substance use, particularly during the adolescent period of heightened neural plasticity, may also exacerbate pre-existing vulnerability or introduce neuroadaptive changes in the developing brain.

Kim-Spoon et al. (2020) make an important addition to the existing literature on adolescent neurodevelopment and substance use. They examined the temporal ordering and bidirectional associations between risk-related neural processing in the insula, behavioral cognitive control, and cigarette, alcohol, and cannabis use in a sample of 167 adolescents assessed annually four times starting at ages 13 to 14 years. They found that greater substance use predicted increases in subsequent insular activation during a risk processing task (i.e., reflecting a bias toward more risky decision making), but not the converse, and further found this effect to be particularly strong in adolescents who scored lower on a behavioral measure of cognitive control. This study has many methodological strengths, including multiple assessment waves during a key developmental period; multimethod assessment that included neuroimaging, a behavioral task, and self-report measures; and the use of latent change score modeling to evaluate longitudinal change. The examination of individual differences in both cognitive control and reward processes is a major strength of this study. That deficits in cognitive control precede substance initiation and problematic use is now well-established. The role of reward for substance use and abuse is less clear, and likely depends on aspects of reward processing (e.g., anticipation versus receipt) and the

phase of the addiction cycle. Although there is evidence of hypoactivation to reward anticipation and hyperactivation to reward receipt among adults with substance use disorders (see Luitjen et al., 2017), whether these reward-related deviations precede problematic substance use and potentially confer causal risk for its development remains unclear. Kim-Spoon et al. (this issue)'s results suggest this is not the case. Instead, their finding that substance use preceded increased insular activation during a risk processing task suggests reward-related brain differences may reflect an effect of substance use on the brain circuitry underlying reward processing. Moreover, their finding of stronger coupling effects from substance use to insular activation among adolescents with lower cognitive control highlights the potentially critical role of cognitive control in the developing addiction process.

Identification of predisposing causal risk factors for and consequences of substance use and abuse informs strategic prevention and intervention efforts, and this paper highlights cognitive control and substance use as potential targets. However, this presumes that deficits in cognitive control confer *causal* risk for substance use and abuse, and that substance use *causes* changes in the insula. Without a counterfactual case, it is not possible to know whether the increased insular activation observed subsequent to substance use would not have also occurred in the absence of substance use. Temporal precedence is necessary for establishing causal relationships among constructs, but it is not sufficient. Establishing causal relationships is not simply an intellectual exercise—it is necessary for effective preventive-intervention. To the extent lower cognitive control reflects a measurable manifestation of a larger underlying liability toward substance use and abuse and related externalizing problems (e.g., behavioral disinhibition; Iacono, Malone, & McGue, 2008), interventions that attempt to, for example, improve cognitive control abilities, will be ineffective for preventing substance use and abuse. Conversely, if substance use precedes, but does not cause, subsequent changes in the brain, interventions that limit substance exposure will be ineffective in preventing these changes.

Understanding causal relationships is critical for informing etiological models and for guiding the most strategic preventive-intervention efforts. But differentiating cause from consequence is not a straightforward task. It is neither feasible nor ethical to directly alter the adolescent brain to increase cognitive control abilities, or to randomly assign adolescents to substance using versus nonusing groups, as in an experiment. Instead, we must rely on study designs that are not true experiments but are still causally informative. These include longitudinal studies, as well as natural experiments, such as twin and family studies (see Rutter, 2007). Each of these study designs has its own unique advantages and disadvantages. Even a well-designed prospective, longitudinal study, such as the one leveraged here by Kim-Spoon et al. (2020), can only establish temporal precedence, not causal precedence. However, we can glean important insights from complementary causally informative study designs. Consider Kim-Spoon et al. (2020)'s findings in conjunction with findings from four other relevant studies. One study found frontostriatal differences among adults with a stimulant use disorder relative to a non-stimulant using control group (Ersche et al., 2012), a result that has typically been interpreted as evidence of an effect of substances on the brain. However, this study also found comparable frontostriatal differences (linked to cognitive control processes) in the non-stimulant using siblings of the stimulant use disorder group,

suggesting these neural deviations instead reflect pre-existing familial liability shared by siblings. Another longitudinal study found a decrease in IQ scores following cannabis initiation and use in two independent adolescent twin samples assessed at ages 11 and 17 years (Jackson et al., 2016). Again, such a result has typically been interpreted as evidence of an effect of substances on neurocognitive functioning. However, this study also found that, among twin pairs discordant for cannabis use, non-using twins showed comparable decreases in IQ scores as their using co-twins, again suggesting the decrease instead reflects shared familial liability. Using a co-twin difference approach in a sample of adolescent twins, my colleagues and I found comparable deviations in brain regions linked to cognitive control processes (e.g., gray matter thickness in frontal regions) among greater substance using twins and their lesser using co-twins, but we also found more risky decision making, indexed by poorer behavioral performance on a gambling task, among greater substance using twins relative to their lesser using co-twins (Malone et al., 2014; Wilson, Malone, Thomas, & Iacono, 2015). By incorporating longitudinal assessments and familial “controls” (siblings, twins) well matched for genetic and early rearing environmental influences, these studies collectively provide converging evidence that lower cognitive control indexes pre-existing liability toward substance use and abuse, but that substance use may have a causal effect on reward processes and underlying brain circuitry.

The investigation by Kim-Spoon et al. (2020) sets the stage for future investigations that will further our understanding of the bidirectional, dynamic, and potentially causal associations between substance use and abuse and the brain circuitry underlying cognitive control, reward, emotionality, and learning/memory processes. One important future direction will be to track the progression from substance initiation to regular use, to misuse, to disorder, as different processes or aspects of these processes may come into play differently at different stages of the addiction process. In that regard, although examination by Kim-Spoon et al. (2020) of both cognitive control and reward processes is a strength, it will also be important in future work to consider additional processes that may confer causal risk for or be affected by substance use and abuse, either individually or in interaction with other processes. Other individual difference, familial, and contextual factors will also be important to consider, such as comorbid psychiatric disorders, parental substance use, trauma and maltreatment, and peer influences. The Adolescent Brain Cognitive Development (ABCD) study (abcdstudy.org), a multisite investigation of over 11,000 children first assessed at age 9 or 10 years, who will be followed up every 6 months for 10 years, through adolescence, holds considerable promise for mapping adolescent neurodevelopment and the developing addiction cycle, as well as familial and contextual factors that confer risk or promote resilience. The ABCD study also includes over 800 twin pairs, which, particularly in the context of its prospective, longitudinal study design, increases causal inference considerably and makes possible investigation of genetic and environmental influences on the developing brain, substance use and abuse, and related risk and protective factors (Iacono et al., 2018). Of note, although adolescence and the transition into emerging adulthood is an optimal time for investigations of substance initiation and the developing addiction process, there is also great potential value in even earlier investigations. The risk processes that lead some adolescents to initiate substance use earlier or misuse substances were in place years earlier, manifested in impulsive, inattentive, dysregulated, and aggressive behaviors evident as early

as the preschool years, if not earlier. Delineating the developmental origins of substance use and abuse to identify the earliest causal risk factors and maximize early prevention efforts will require causally informative investigations well before adolescence.

In conclusion, Kim-Spoon et al. (2020) are to be commended for their investigation of prospective associations between neurodevelopment and substance use in adolescence, the importance of which has since been recognized by the National Institutes of Health in their launching of the ABCD study. Causally informative study designs, including prospective, longitudinal studies, as well as twin and family studies, are necessary for answering vexing but critical questions about substance use and the developing brain. Investigations that seek to differentiate cause from consequence and identify the factors that initiate the cycle of addiction have the potential to transform our understanding of the development of substance use and abuse, prompt revisions to current models of addiction, guide the most strategic preventive-intervention efforts, and ultimately improve the lives of millions of affected individuals and their families.

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