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Editorial

Drugs, mental health and the adolescent brain: implications for early intervention

Early onset or frequent substance use during adolescence is consistently associated with a wide range of adverse outcomes, including mental health problems.[1,2] For example, recent meta-analytic studies suggest that cannabis use is associated with increased risk for later psychosis, with clear evidence of a dose-response effect.[3,4] There are also data to suggest that the risk is even greater if cannabis exposure occurs during adolescence.[5] Moreover, compared with non-substance-using peers, teenagers who smoke tobacco regularly appear to experience greater mental health problems in older adolescence,[6] while those who abuse alcohol have higher rates of mental disorders and attempted suicide.[1,7] While the epidemiological link between early onset substance use and later mental disorder is well described, the specific neurobiological mechanisms that underpin this relationship remain elusive. In this editorial, we discuss recent evidence highlighting neurodevelopmental harms associated with adolescent substance use, and outline the implications of such findings for prevention and early intervention approaches.

IMPACT OF ADOLESCENT SUBSTANCE USE ON NEUROBIOLOGICAL PROCESSES

Preclinical studies clearly demonstrate that substance use during adolescence has ongoing neurodevelopmental harms, including altered sensitivity to later drug exposure, impaired cognitive functioning and cortical damage.[8] There is also growing evidence that psychoactive substances impact differentially on both behaviour and brain function during adolescence. For example, cannabinoid exposure has been found to have greater anxiogenic, aversive and locomotor-reducing effects in adult compared with adolescent rats,[9] whereas adolescent rodents exhibit less sensitivity to the initial effects of high dose toluene (an organic solvent that is commonly abused) compared with adults, and demonstrate less sensitization with repeated exposure.[10] Adolescent rodents are also able to maintain their balance at significantly higher inclines on a tilting plane (a glass surface that is slowly raised at one end) than adults when given increasing doses of alcohol, suggesting they are *less* sensitive to alcohol's effects on balance and motor coordination.[11] If adolescent animals are less sensitive to some of the behavioural effects of acute drug use, this may mean that young people are able to use substances at higher doses for longer periods than their adult counterparts. But does the ability to party harder come at a cost?

Although adolescent animals appear to be less sensitive to some behavioural effects associated with acute drug use, there is growing evidence that they are *more* sensitive to their neurotoxic properties. For example, adolescent rodents are more vulnerable than adults to the effects of alcohol on both memory and memory-related brain function, a finding that might stem from the adverse effects of alcohol on the development and maturation of brain regions such as the hippocampus.[12,13] Quinn *et al*. recently demonstrated that while adolescent rodents find repeated cannabinoid exposure less aversive than adult rats, they display greater residual cognitive deficits and hippocampal alterations.[14] Similarly, Cha *et al*. reported that both acute and extended cannabinoid exposure impairs spatial and non-spatial learning in adolescents more than adults.[15] Brief episodic exposure to nicotine in adolescent rodents (mimicking human patterns of use) has also been shown to produce lasting cellular and neuritic damage, even at plasma concentrations one-tenth that observed in regular smokers.[16] Importantly, these findings were not replicated in adult animals, even after exposure to higher plasma concentrations for extended periods.

Few human studies have examined the impact of substance use on neurobiological processes, although most findings are consistent with the animal literature. A number of small cross-sectional studies have found that adolescents and young adults with alcohol use disorders demonstrate smaller hippocampal volumes than healthy matched controls,[17,18] as well as smaller prefrontal cortices and white matter volumes.[19] These studies also demonstrate an association with duration of use and measures of alcohol consumption, and are consistent with reported alcohol-related

neurocognitive impairments among adolescent drinkers.[20] Young people who begin using cannabis before the age of 17 also appear to be more vulnerable to cognitive impairments and show reduced brain grey matter.[21,22]

ADOLESCENT BRAIN DEVELOPMENT

Such findings are concerning, and suggest that teenage substance use may increase risk for mental disorder by disrupting neural development in regions critically involved with cognitive and affective function. In fact, adolescence encompasses an extensive period of neural maturation, particularly in areas associated with core executive and self-regulatory skills, such as inhibitory control and affect-regulation.[23] Initial increases in cortical grey matter volume during childhood is followed by extensive pruning of cortical synapses and increased myelination during adolescence and early adulthood.[23] This pruning of excess synaptic connections results in a refinement of the neural circuitry, such that communication across distributed systems is vastly improved. However, these processes do not appear to occur uniformly across the brain at the same rate. While the more posterior and deep brain structures mature during childhood and early adolescence, increased maturation within the frontal and temporal cortices, as well as the cerebellum (brain regions most consistently implicated in the neurobiology of mental disorder) occur later in adolescence. Interestingly, the peak age of onset for many psychiatric disorders are in keeping with the timing of these later maturational changes,[24] suggesting that aberrant developmental processes related to fronto-temporal and cerebellar regions may contribute to the expression of psychopathology. In line with this notion, recent neuroimaging studies in at-risk cohorts have identified greater cortical grey volume loss among individuals who develop psychosis,[25,26] suggestive of an accentuated pruning process.

The process of myelination also does not occur concurrently in all brain regions – there is a graded progression of maturation from inferior to superior and posterior to anterior, with the cerebellum developing first and the frontal lobes last.[23] Although few studies examining the impact of substance use on myelination have been conducted, Bartzokis and colleagues reported that chronic cocaine use substantially interferes with normal white matter maturation, particularly within frontal and temporal brain regions.[27] If adolescent substance use directly impacts upon the development of fronto-temporal white matter circuits, this may increase the risk for mental disorder by affecting memory, executive and affective functioning.

POTENTIAL CONFOUNDS

To what extent such findings may be explained by the effects of substance use on the developing brain or the neurobiological characteristics of those young people who begin using at an early age (or a combination of the two) remains to be determined. In this regard, research examining the impact of substance use on adolescent development must consider whether there is evidence for premorbid neurobiological vulnerabilities among early onset users. Although limited, there are some data to suggest that impairments in frontal functioning are evident in high-risk populations (e.g. family history of alcohol abuse) prior to drug use exposure,[13,28] and that cortical pruning processes may also be delayed.[29] In addition, many young users have experienced childhood mistreatment, which in itself has been shown to affect brain development.[30] Early severe stress has been found to induce persistent alterations within the hypothalamic-pituitary-adrenal axis as well as multiple neurotransmitter systems, resulting in pruning anomalies and delays in myelination.[30] Together, these findings highlight the urgent need for prospective studies of adolescent development (prior to the onset of drug experimentation) that systematically examine changes within brain structure and function longitudinally, and that appropriately control for a history of childhood mistreatment or familial substance misuse.

IMPLICATIONS FOR PREVENTION AND EARLY INTERVENTION

Improved understanding of the neurobiological links between adolescent substance use and mental disorder, as well as the impact of adolescent substance use on cognitive, emotional and brain development, will reinforce existing evidence of the developmental harms associated with adolescent substance use,[1] and the need for well-resourced prevention and early intervention programmes.[31,32] Reducing substance-related morbidity among young people requires a sophisticated, systematic approach, incorporating a broad range of strategies that target (i) delaying the age of onset of drug experimentation (e.g. economic and regulatory measures, parent and school-based education, social marketing, health promotion); (ii) reducing

the number of young people who progress to regular use (e.g. preventive screening, brief interventions); and (iii) encouraging current users to minimize or reduce risky patterns of use (e.g. psychosocial and pharmacological interventions).[2,32] Indicated prevention programmes that target young people at high risk for harmful substance use (e.g. children and adolescents in families with drug-using parents, young people who have been suspended from school or have mental health problems) are also essential,[2] particularly as they are likely to have premorbid neurobiological vulnerabilities.

While delaying the age that licit drugs can be legally purchased is an effective strategy for reducing early age substance use, regular adolescent use and related harms, such campaigns often face serious political barriers.[1] Clear evidence of differential neurobiological harms during adolescence will bolster calls for a more responsible alcohol policy and legislative framework, as well as the development of guidelines for parents regarding appropriate adolescent alcohol use. Such information will also better inform young people, who continue to use substances despite an apparent awareness of the links between substance use and mental disorder.[33] Indeed, rather than focus on the adverse effects of psychoactive substances, public health campaigns should promote the potential health benefits of delaying or minimizing risky use (e.g. preventing mental disorder, ensuring optimal brain development) and attempt to reduce the social acceptability of such use, as well as encourage positive self-help strategies and coping skills.

Effective early identification and intervention for adolescent substance use is an important strategy for reducing long-term drug harms, as well as the primary prevention of mental disorder. Although limited work has been conducted related to the impact of prolonged abstinence on adolescent brain function, it seems likely that younger brains may have a greater capacity for recovery, further highlighting the importance of early intervention approaches. Nevertheless, there is clear evidence that young people who seek treatment for their mental health issues as well as those with a strong family history of mental disorder should be provided with information regarding the neurobiological link between mental illness and substance use, as well as brief interventions that discourage regular use (i.e. primary prevention of secondary disorder). In addition, youth-specific health services that acknowledge the interplay between substance use and mental disorder and their neurobiological and psychosocial associations, and that provide relevant integrated approaches to treatment are essential for ensuring that the needs of young people are appropriately met in a timely and comprehensive manner.

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