

## Commentary

## Adolescent Cannabinoid Use and Cognition; Unexpected Results from a Rat Model of Cannabinoid Self-Administration

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Cannabis is the most widely used illicit substance in the United States and worldwide, and its use is expected to increase with recent and pending changes in its legal and medical status. Cannabis use during adolescence is of particular concern because of its association with enduring cognitive impairments and overall worse life outcomes. Whether these deleterious outcomes are a direct result of cannabis use, however, remains controversial (Curran *et al*, 2016). Indeed, many of the genetic and environmental factors that increase the likelihood of drug experimentation (eg, impulsivity, low socioeconomic status, and chronic stress) also predispose individuals to adverse outcomes, even in the absence of drug use. Animal studies to date, however, also show that cannabinoid administration during adolescence can induce cognitive deficits that persist into adulthood. While directly addressing causality, these prior animal studies also have limitations, as they have employed passive drug administration, which fails to model the volitional nature of human drug use. This is an important distinction as passive versus active drug administration can result in unique neural and behavioral consequences. Self-administration models (in which a response is required in order to receive a drug) better mimic human drug use, but cannabinoid self-administration can be challenging to establish. In this issue of *NPP*, Kirschmann *et al*. report the first animal model of adolescent cannabinoid self-administration. Rats in this study were trained to intravenously self-administer the synthetic CB1 receptor agonist WIN55,212-2 (WIN) in daily sessions over several weeks during mid- to-late adolescence. The rats acquired robust WIN self-administration at levels comparable to those shown previously in adult rats (Fattore *et al*, 2007).

A primary goal of these studies was to evaluate the effects of adolescent cannabinoid self-administration on adult

cognitive outcomes. Rats that self-administered WIN during adolescence, together with control rats that had comparable experience self-administering a food reward, were assessed under drug-free conditions on several tests of prefrontal cortex (PFC)-dependent mnemonic function (delayed-response working memory and spatial/object recognition memory tasks). Somewhat surprisingly, cannabinoid self-administration had no adverse effects on performance across a range of adult time points, and working memory performance was actually enhanced. These findings stand in sharp contrast to the cognitively impairing effects of passive adolescent cannabinoid exposure reported previously, and suggest that the route of administration has a critical role in behavioral consequences of cannabinoids. It is also important to acknowledge, however, that the cumulative doses of self-administered WIN were markedly lower than doses used in prior passive administration studies. Indeed, Kirschmann *et al*. replicated a previous demonstration of impaired spatial and object recognition memory following passive administration of higher WIN doses (Abush and Akirav, 2012). It is possible that these and similar impairments are due to the increased anxiety reported to follow passive, high dose cannabinoid administration. It remains to be determined whether passive administration of doses more akin to those achieved through self-administration produces such deleterious behavioral effects.

The most surprising result from Kirschmann *et al*. was the enhanced working memory following adolescent WIN self-administration. This enhancement was evident both 20 and 60 days following drug cessation, and was accompanied by biochemical evidence for an enduring shift in the normal balance of excitatory and inhibitory signaling in PFC. Prefrontal cortical excitatory and inhibitory circuit and signaling dynamics are essential for working memory, and GABAergic signaling dysfunction in particular is increasingly recognized as a contributor to working memory impairments across a range of conditions (McQuail *et al*, 2015). In the current study, rats that self-administered WIN showed increased adult PFC expression of the R2 subunit of the GABA<sub>B</sub> receptor (GABA<sub>B</sub>R2), and of the primary

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neuronal transporter for GABA, GAT-1. This GAT-1 upregulation, and consequent increased efficiency in GABA clearance, might be expected to facilitate the sustained pyramidal neuronal activity required for information maintenance, thereby contributing to enhanced working memory performance. The fact that GABA<sub>B</sub>Rs are localized to both pre- and post-synaptic sites makes it difficult to speculate regarding the specific synaptic consequences of the increased GABA<sub>B</sub>R2 expression. Nevertheless, this finding certainly suggests that there is increased surface expression of GABA<sub>B</sub>Rs associated with adolescent cannabis use. Despite remaining questions regarding specific mechanisms, the fact that such robust alterations in GABAergic signaling protein expression were present well after cessation of drug use highlights a critical need to better elucidate how cannabis use in adolescents alters PFC GABAergic signaling parameters, and to further define the degree to which such effects endure across the lifetime. Single-cell analyses of PFC circuit dynamics, together with the biochemical and behavioral approaches employed by Kirschmann *et al.*, could help clarify the cellular mechanisms whereby cannabis impacts GABAergic signaling and determine the circumstances under which cannabinoids can benefit (or harm) cognition.

Despite the absence of cognitive impairments resulting from WIN self-administration, the take-home message should not be that adolescent cannabis use is harmless. In addition to GABAergic signaling alterations, WIN self-administration also produced robust cue-induced reinstatement following extended extinction, which increased in magnitude following extended abstinence (ie, incubation of craving (Pickens *et al.*, 2011)). These latter data highlight the potential of cannabinoid cues to promote continued use throughout the lifespan. Indeed, ongoing consumption may be a key variable in the long-term cognitive consequences of cannabis use (Curran *et al.*, 2016).

The results of Kirschmann *et al.* represent an important step in modeling adolescent cannabis use and its long-term consequences, but as with any such first step, many questions remain unanswered. For example, it remains to be seen how adolescent WIN self-administration influences affective behaviors (eg, depression- and anxiety-like measures) that

are altered by passive administration. In addition, future studies that build on Kirschmann *et al.* to incorporate a range of drug doses, both sexes, and additional rat strains, will help shape the conclusions regarding the long-term consequences of cannabis use in adolescence. These latter two variables in particular may be relevant for future research in this area, as females may be more sensitive than males to cannabis and cannabinoid administration (eg, (Fattore *et al.*, 2007; Wiers *et al.*, 2016)) and at least one report suggests that adult rats of the strain employed by Kirschmann *et al.* (Sprague-Dawley) self-administer WIN less readily than other strains (Fattore *et al.*, 2007). These issues notwithstanding, the current results provide a critical advance toward a preclinical research agenda on adolescent cannabis use.

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The authors declare no conflicts of interest.

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