

Determining the Ontogeny of Working Memory and Effects of Cannabinoid Self-Administration in Adolescent Rats

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Adolescence is characterized by risky behaviors like drug-taking, and marijuana (*Cannabis sativa*) use is widespread. In addition, adolescence is a period of neurodevelopment in the prefrontal cortex (PFC), a key regulator of cognition and inhibitory control, and thus there is potential for adolescent cannabis use to cause long-term effects on cognitive function. Though some rodent and primate research does show evidence of cognitive deficits after experimenter-administered cannabinoids during adolescence, it remains unknown whether similar deficits occur in a model of drug use and addiction – cannabinoid self-administration. Thus, we sought to determine the ontogeny of working memory across adolescence and the long-term effects of cannabinoid self-administration during this critical period.

Methods: In order to understand what effects cannabinoid self-administration has on cognition, we first identified the critical period for the development of working memory in adolescent male Sprague-Dawley rats. We then established intravenous self-administration of the synthetic cannabinoid agonist WIN55,212-2 (WIN) in adolescents and examined the long-term effects of cannabinoid self-administration during adolescence on working memory performance. The ontogeny of working memory was assessed by comparing performance in adolescent (starting on postnatal day 28; p28; n=12) and adult (>p70; n=8) rats on a delayed-match-to-sample working memory task with equivalent training history. Separate groups of rats were trained to self-administer WIN (n=24) or sucrose (controls; n=23) in daily 2- or 6-hr sessions during adolescence (p38-52). Working memory performance was then assessed beginning 20 days later (in adulthood), and changes in protein expression in the medial prefrontal cortex were determined by Western blot.

Results: Daily comparison of working memory performance found that adolescent performance was consistently worse than adults when the delay between sample and response was long. A significant difference by age was observed up to p46, and adolescent performance did not reliably overlap adults until late adolescence (p51). There was no effect of age on acquisition of nose poke responding or on performance when there was zero delay between sample and response. Rats readily acquired self-administration of both WIN and sucrose, and exhibited significant cue-induced reinstatement to both reinforcers after extinction. The WIN group also demonstrated an “incubation of craving” effect with significantly greater cue-induced responding on day 21 vs. day 1 of abstinence. Surprisingly, both short- and long-access WIN self-administration in adolescence produced significant improvements in adult working memory performance. In addition, we found significant differences in the expression of GABAergic and glutamatergic signaling proteins in the mPFC of the short access WIN self-administration group, indicating that self-administered WIN can produce long-term consequences on cortical development.

Discussion: Taken together, our findings suggest that working memory becomes adult-like in late-adolescence; that adolescent cannabinoid self-administration does produce addiction-like effects, but that a self-administered cannabinoid does not produce long-lasting working memory deficits.

Funding was provided by NIH grant K01DA031745 and the Pennsylvania Department of Health.