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Research Article

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Effects of adolescent cannabinoid administration in mice on behavioural inhibition and susceptibility to stress during adulthood

Abstract

Background: Cannabis is one of the most frequently used substances by adolescents. Early exposure to psychoactive compounds has been shown to alter normal brain development and has consequences for psychiatric illness and behaviour in adulthood. In this study, we explored the effects of adolescent synthetic cannabinoid exposure on susceptibility to stress in adulthood, in addition to changes in impulsive behaviour.

Methods: Chronic treatment with synthetic cannabinoid WIN55,212-2 (WIN) at various doses in adolescent mice was followed by the chronic social defeat stress paradigm in adulthood to assay changes in susceptibility to stress. We then employed the operant Go/No-Go task to investigate changes in impulsivity.

Results: No changes in susceptibility to stress were identified ($\chi 2(3)=0.585$, $p=0.900$). Strikingly, we demonstrated a dose dependent decrease in impulsivity of adolescent WIN-treated subjects as measured using the Go/No-Go task ($F(3, 20)=5.743$, $p=0.0053$).

Limitations: The main limitation of our findings is the small sample size, particularly for assaying changes in susceptibility to stress using the chronic social defeat stress paradigm. Furthermore, the single housing of animals and suboptimal performance of controls may have affected our findings in the Go/No-Go task.

Conclusion: Overall, this study presents a novel behavioural finding consequent to adolescent exposure to cannabinoids. Further research into the long-term effects of cannabinoid use in adolescence is needed, especially in light of its prevalent use and legalization in Canada.

Background

Cannabis is a psychoactive compound which has been legalized for recreational use in Canada. (1) Considering the subsequent increase in cannabis usage rates among adolescents (2), it is important to consider the consequences of exposure to cannabinoids during this critical period. (3–7) Neurobiological changes that occur during adolescence critically influence the development of healthy behaviours and psychiatric health. (8,9) Evidence from humans and animal models suggests that adolescent usage of drugs of abuse has lasting impacts on the development of the brain such as notable changes in cognitive features and increased susceptibility to stress in adulthood. (3,4,10,11)

There are many studies which address the consequences of adolescent cannabis use on a population level as they relate to neuropsychiatric illness. A large Swedish conscript registry study identified baseline cannabis use as a prominent risk factor for any psychotic symptom, rigorously demonstrating the population level association of cannabis with psychotic illness. (6,12–14) On the spectrum of stress-related disorders, Gobbi et al.'s 2019 systematic review and meta-analysis showed an association between cannabis use in adolescence and development of depression or suicidality in young adulthood. (11) Smolkina et al. in 2017 applied modelling to twin-registry studies including subjective reports, and even suggested a causal association between cannabis use disorder and major depressive disorder. (15) These studies demonstrate the importance of investigating the mechanisms behind how cannabis affects the developing brain. Findings from these studies may inform public health dissemination surrounding cannabis use in adolescence.

The endocannabinoid system is known to be involved in many aspects of neurodevelopment, including normal formation of synapses and plasticity. (16) Cannabis is more complex than other drugs of abuse with respect to its cognitive effects and the number of molecular pathways it modulates (16,17). Δ^9-Tetrahydrocannabinol (THC), the psychoactive component of cannabis, interacts with the endocannabinoid system in ways. It is challenging to determine whether THC administration will be excitatory or inhibitory at a neuronal level; factors such as local receptor density and temporal dynamics mediate the efficiency and valence of THC-mediated neurotransmission. (16) Since THC is a partial agonist of Cannabinoid receptor type 1 (CB1R) and Cannabinoid receptor type 2 (CB2R), in the present study we use the synthetic cannabinoid WIN55,212-2 (WIN), an agonist of CB1Rs, to isolate the effects of exogenous agonism of the endocannabinoid system. WIN has been used in numerous studies for its exceedingly high binding affinity for the CB1R when compared with that of THC. The endocannabinoid system modulates the development of the prefrontal cortex, known to be a major center for cognitive development during adolescence. (18) Consequently, studying the effect of agonism at CB1Rs during adolescence may shine light on persisting behavioural changes into adulthood.

Through human neuroimaging studies, cannabis use in adolescence has been shown to cause functional differences in the prefrontal cortex. Some studies suggest chronic cannabis users have decreased gray matter in the hippocampus and increased amygdalar volume, in addition to aberrant signalling in the nucleus accumbens, amygdala, and the prefrontal cortex. (19,20) These systems are strongly involved in memory, emotional regulation, and cognitive behaviours. Further, Miller et al. demonstrated that chronic adolescent administration of THC altered morphology of and transcriptional trajectories in cortical neurons. (21) Because insult to the endocannabinoid system is expected to alter prefrontal cortex development, this study examined a cognitive function associated with this area. Behavioural inhibition and impulsivity are known to be associated with the medial and dorsolateral prefrontal cortices. (22,23) The prefrontal cor

tex forms circuits with the posterior parietal cortex and supplementary motor areas to direct these behaviours, whose transmission is dominated by glutamatergic and dopaminergic inputs. (22)

There are a handful of studies which address similar behavioural questions. These studies use comparable tests of impulsivity and behavioural inhibition, such as the impulsive choice in a delayed reward paradigm, reversal learning, or response inhibition in a stop-signal paradigm. (24,25) Pattij et al. were interested in the acute effects of WIN on impulsive behaviour in decision making paradigms and found that they did not differ from controls. (25) In a paradigm very similar to our own, Johnson et al. chronically treated adolescent and adult rats with WIN and tested them on a battery of cue reversal-based tasks in adulthood. They found that adult, but not adolescent, experimental subjects had impaired behavioural inhibition. (24) Despite these results, we are interested in assaying this behaviour in a different behavioural paradigm.

In two parts, this study examines how adolescent synthetic cannabinoid exposure affects both susceptibility to stress and impulsive behaviour in a murine model. Given the demonstrated cortical changes in response to cannabinoid exposure, we hypothesized that exogenous modulation of the endocannabinoid system in adolescence could be associated with altered susceptibility to stress and behavioural inhibition in adulthood. We employed a chronic social-defeat stress model in mice to evaluate differential susceptibility to stress. In addition, the operant Go/No-Go paradigm was used to investigate changes in impulsivity across WIN treatment groups. This study is especially relevant since cannabis use is prevalent in adolescents.

Methods

Study Overview

A between-subjects design consisting of treatment with WIN, exposure to Chronic Social Defeat Stress (CSDS), and testing in Go/No-Go was used to address the hypotheses posited. The experimental strategy is detailed in Fig. 1. Fig. 2 describes the subjects of the study and their allocation to experimental groups. Only animals who did not undergo CSDS were tested in the Go/No-Go paradigm.

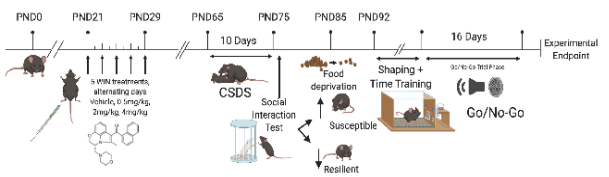

Figure 1. Timeline and schematic of study conducted. WIN55-212,2 treatment in adolescence, defeat paradigm and behavioural assessments, and Go/No-Go tasks.

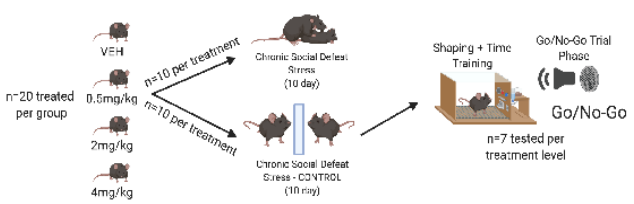

Figure 2. Subjects of the study, and their random allocation to experimental groups. 20 subjects treated with Vehicle, 0.5mg/kg, 2mg/kg, or 4mg/kg. 10 from each treatment group allocated to defeat or no-defeat, and 7 no-defeat subjects allocated to Go/No-Go tasks.

Ethical Considerations and Animal Information

The study was performed in accordance with the guidelines of the Canadian Council of Animal Care and approved by the McGill University and Douglas Hospital Animal Care Committee under Animal Use Protocol #5084. All mice used as subjects were obtained from Charles River Canada and were maintained on a 12 h light-dark cycle (lights on 8h00) with ad libitum access to food and water at all stages except during weight restriction for Go/No-Go.

Design and Subjects

The study included four groups: three treatment groups with 0.5 mg/kg, 2 mg/kg, and 4 mg/kg of WIN, and a vehicle (VEH) control. Twenty male C57BL/6 mice were treated per group (n = 20) and housed in groups of four. Subsequently, ten animals were randomly assigned to the defeat or non-defeat condition (n = 10). From the non-defeat condition, seven subjects from each of the four groups were randomly selected to perform the Go/No-Go task (n = 7). (Fig. 2) After the chronic social defeat stress paradigm, animals were singly housed until study completion. In sum, the study consisted of eighty mice. Deaths and exclusions from results are justified in Appendix 1.

WIN Treatment

Dosages used in this study include 0.5 mg/kg, 2 mg/kg, and 4 mg/kg of WIN. WIN was solubilized in 18:1:1 0.9% saline:cremophor:ethanol. Early adolescent mice were treated with saline or WIN via intraperitoneal injections from postnatal day (PND) 21 to PND29 between 12h00-13h00. Consistent with our previous experiments, groups received doses every other day in the same timeframe while alternating injection side for a total of five doses. Mice were returned to their cages upon drug administration. Although no rigid margins exist for this critical developmental period, the literature suggests that the period between weaning and PND32 comprise early adolescence due to distinct neurobehavioural traits exhibited. (9,26–28)

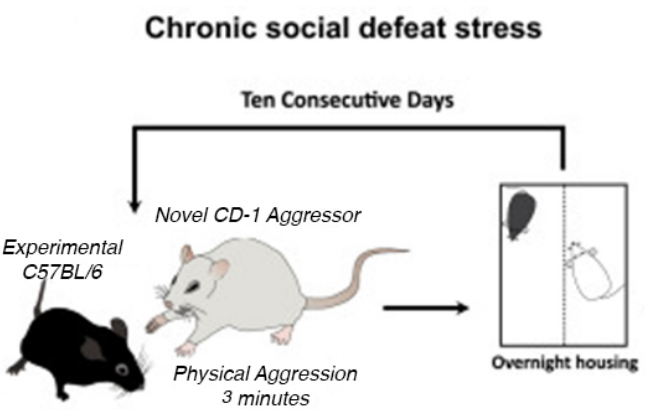

Figure 3. Flow of the CSDS model. Figure adapted from Torres-Berrió et al. 2019. C57BL/6 mice are subject to physical aggression from a novel CD1 aggressor mouse for 10 consecutive days. Overnight, they are housed with their aggressor from the preceding day with sensory but no physical contact.

Chronic Social Defeat Stress (CSDS)

The CSDS paradigm is a reliable method to produce stress-related phenotypes in mice and is widely used in mouse studies of susceptibility to stress. (29,30) The protocol was performed as in (30–32) and consisted of 10 daily sessions in which adult (PND65) subjects were exposed to 3 minutes of physical aggression by a novel aggressive CD-1 mouse, followed by overnight housing of the subject and the aggressor as shown in Fig. 3. The mice were separated by a perforated cage partition which allows for sustained

Control C57BL/6 mice were housed with a different control mouse every day, and no physical contact was permitted. Twenty-four hours after the final CSDS session, subjects were assessed on the social interaction test to determine whether the paradigm produced stress-related phenotypes.

Social Interaction Test (SIT)

To classify whether a subject was susceptible to stress, we assessed social preference using the social interaction test. The SIT was conducted as in. (30) In the first part of this test, subjects explore an open-field arena (42cm x 42cm) in the absence of a CD-1 mouse for 2.5 minutes. The second part involves a novel CD-1 mouse contained within a mesh cage in the same arena for 2.5 minutes. The social interaction ratio (SIR) is calculated by dividing time spent in the interaction zone with/without CD-1. The corner time ratio (CTR) is similarly calculated for time spent in corners. A subject is classified as susceptible if they spent less (SIR<1, CTR>1) or resilient if they spent more time socializing (SIR>1, CTR<1) compared to baseline (ratio = 1). (32)

Go/No-Go

Cognitive changes were assessed using a Go/No-Go task, as performed in previous studies. (27,33–35) Seven subjects from each treatment level (taken from controls in CSDS) were used in the Go/No-Go experiment to assess behavioural inhibition and impulsivity. Briefly, mice were food restricted for the duration of the behavioural testing, such that they maintained 85% of initial free-feeding weight. The task took place in operant behavioural boxes (Med Associates, Inc., St. Albans, Vermont). The boxes contained a house light, two illuminated nose poke holes, an adjustable tone generator, and a pellet dispenser. Chocolate-flavored dustless precision pellets (BioServ, Inc., Flemington, New Jersey) were used as the operant reinforcer. The experimental procedure consisted of three stages: conditioned reinforcement training, reaction time training, and the Go/No-Go task. Animals were subjected to one training or testing session per day, at approximately the same time daily.

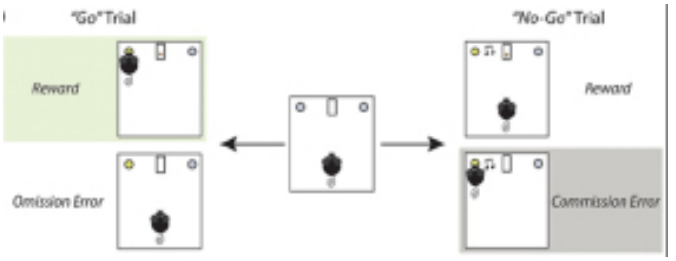

Figure 4. Coding of behaviours in the trial phase of Go/No-Go. Figure adapted from Cuesta and Restrepo-Lozano et al. 2019. Correct responses on the Go-trial are coded as hit, whereas lack of response to cue coded as an omission error. On No-Go-trials, abstention of behaviour results in reward, whereas response results in a commission error.

The subject is driven by hunger to pay attention and drive an association between cue-light and pellet reward. Once the task is learned by the subject, it is taught to respond quickly by shortening the window of successful response to the cue. Following successful completion of both training stages, mice underwent 16 sessions of the Go/No-Go task. Although 10 sessions were planned, the trial was extended to 16 days to assess behavioural differences. This task requires mice to respond to a "go" cue, identical to the cue they were trained on, or to inhibit their response to this cue when it is simultaneously presented with an auditory "no-go" cue (85dB tone). In the go trials, mice had 3 seconds to respond to the cue to receive a reward. This was coded as a "hit" in our analyses. In the no-go trials, the paired tone with the light cue signals the mouse to withhold from responding. If mice responded during the no-go trial, an inter-trial-interval is initiated, and no reward is dispensed. This counted as a "commission error" in the analyses. If mice withheld their response to the light cue on a no-go trial, a reward was dispensed. Within each session, the number of go and no-go trials is given an approximately 1:1 ratio and presented in a randomized order. Each session is 30 minutes in duration and consists of 30-50 of both go and no-go trials. Graphical description of behavioural coding for analysis is described in Fig. 4.

Data Analyses

Analyses were conducted by experimenters blinded to subject identity and treatment group. Preliminary data processing was conducted using Microsoft Excel. Visualisation and figure preparation were performed using Graphpad Prism 8.1. Sigmoidal curve fitting and associated statistical testing for Go/No-Go results were performed using OriginLab.

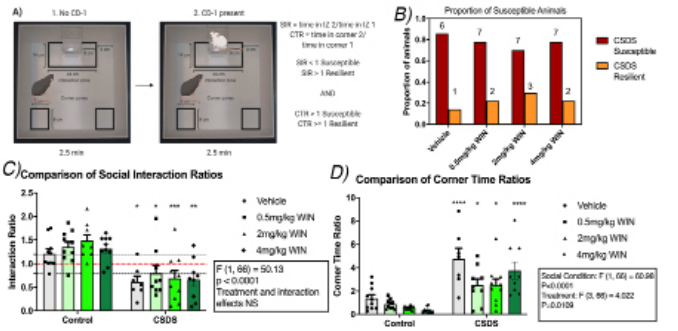

Figure 5. Susceptibility results from Social Interaction Test. A) Graphical description of the social interaction test. In brief, subject spends time exploring the arena, then, explores the arena with a CD-1 present. B) Proportion of susceptible and resilient animals by treatment group. C) SIR plotted for treatment groups compared by CSDS condition. D) CTR plotted for treatment groups plotted by CSDS condition. Mean +/- SEM. p-values: *<0.05, **<0.01, *** <0.001, ****<0.0001.

Results

Susceptibility to Stress

To address whether mice treated with WIN in adolescence were susceptible to stress, we compared the proportion of susceptible animals from each treatment level. The sample proportions of susceptible animals were roughly equal, failing to reject the null hypothesis (23=0.585, p=0.900). Graphical representation is found in Fig. 5B.

Social Interaction Test

To investigate the effect of WIN treatment level and the effect of CSDS on social interaction in the subjects, Two-Way ANOVAs were conducted. Treatment group (level of WIN) and CSDS condition were used as the factors, and SIR and CTR were the dependent variables. CSDS indeed produced a stress-susceptible phenotype by decreased interaction time and increased time spent in the corners for all treatment groups. (Fig. 5C-D) The significant difference and independence of samples indicated in the ANOVA allowed for Sidak's post-hoc comparisons, which validated the production of stress-susceptible phenotypes using the CSDS model.

Go/No-Go

Fig. 4 graphically depicts how a subjects' actions are coded in the trial phase of Go/No-Go. The assumption for assessing behavioural inhibition on this task is that sustained commission errors indicate increased impulsivity or decreased behavioural inhibition. The data is modeled in a few

ways to glean such information. In addition to plotting proportional commission errors over time, we use a pooled efficiency formula, an index of successful learning, to identify the proportion of trials (go or no-go) where the mouse performs correctly. Pooled efficiency is calculated by taking the mean of proportional hits and correct omissions on no-go. Another way to analyze such results is to iteratively fit sigmoidal curves for each subject on their proportional commission errors and determine an equation that best reflects each experimental group. This method is advantageous, as identifying M50 (day at which they reach 50% of their total learning) allows for comparison on relative inhibitory learning rates. It also provides a lower asymptote to their learning, which stands proxy for the level of total motor inhibition.

Go/No-Go – Commission

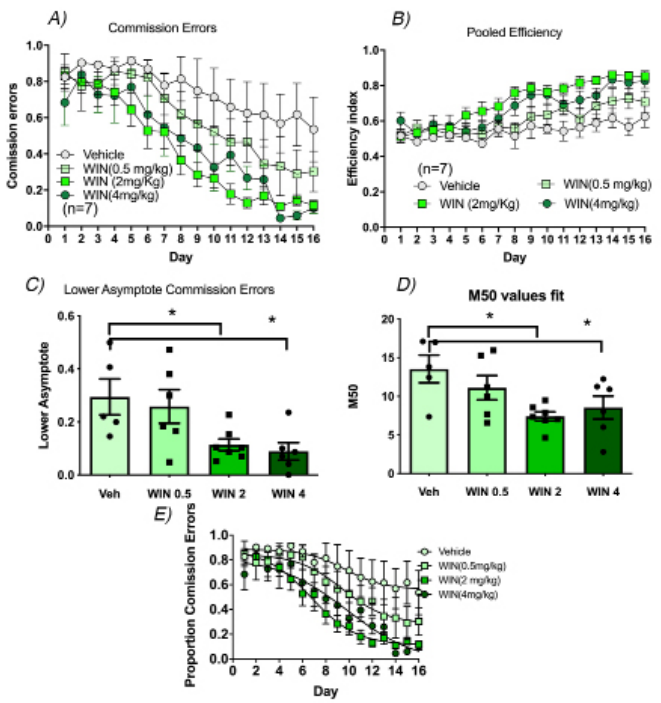

Figure 6. Summary of Go/No-Go results over 16 day trial period. A) Proportional commission error over time. B) Pooled efficiency over time. C) Sigmoidal curve fitting to commission errors. D) M50 group comparison. E) Lower asymptote group comparison. Mean +/- SEM. p-value * <0.05

In plotting commission errors over time, a Two-Way Repeated Measures ANOVA identifies the effect of treatment, days learning, as well as any potential interaction effect. Summary of the F-tests conducted are found in Table 1. There were main effects for both time F(15, 300)=33.34, p<0.0001 and WIN treatment F(3, 20)=3.843, p=0.0254; however, no statistical interaction effect was found F(45, 300)=1.286, p=0.1147. Treatment with 2 mg/kg and 4 mg/kg of WIN significantly decrease commission rates, whereas 0.5 mg/kg treated animals do not differ from vehicle control. Proportional commission errors resultantly suggest improved behavioural inhibition at high WIN doses during adolescence. Proportional commission errors for all groups are plotted in Fig. 6A, and significance for each treatment level in Supplementary Fig.1. There is no difference in proportion of omission errors across treatment groups.

Go/No-Go – Pooled Efficiency

Statistical analysis of the Pooled Efficiency measure is identical to that for proportional commission. Summary of F-tests conducted are found in Table 1. There were main effects for time F(15, 300)=24.12, p<0.0001 and WIN treatment F(3, 20)=5.743, p=0.0053, as well as a statistical interaction effect observed (indicating presence of an extraneous variable) F(45, 300)=1.882, p=0.0011. Like the report of commission errors, 2 mg/kg and 4 mg/kg WIN-treated animals outperformed vehicle controls, and this effect was more pronounced for the 2 mg/kg group. Pooled Efficiency for all groups is plotted in Fig. 6B.

Go/No-Go – Curve Fitting

Fig. 6C depicts the sigmoidal curves describing proportional commission errors. This mathematical model allows for the analysis of new parameters on behaviourally relevant dimensions. With smaller M50 values indicating more rapid inhibitory learning, a One-Way ANOVA revealed statistically different learning rates described in Supplementary 2. Tukey's HSD post-hoc comparison of these independent observations echoed previous findings; WIN 2 mg/kg and 4 mg/kg groups learned significantly faster in comparison to the vehicle group. When applying similar analyses to the lower asymptote, increased motor inhibition was observed in the high dose WIN groups. These parameters are depicted graphically in Fig. 6D and E, respectively. Statistics for M50 and lower asymptote can be found in Supplementary Material 2.

Commission Two-Way RM ANOVA

Source of Variation	P value	P value summary	Significant?	F (DFn, DFd)	P value
Time x Drug	0.1147	ns	No	F (45, 300) = 1.286	P=0.1147
Time	<0.0001	****	Yes	F (15, 300) = 33.34	P<0.0001
Drug	0.0254	*	Yes	F (3, 20) = 3.843	P=0.0254
Subject	<0.0001	****	Yes	F (20, 300) = 16.51	P<0.0001

Pooled Efficiency Two-Way RM ANOVA

Source of Variation	P value	P value summary	Significant?	F (DFn, DFd)	P value
Time x Treatment	0.0011	**	Yes	F (45, 300) = 1.882	P=0.0011
Time	<0.0001	****	Yes	F (15, 300) = 24.12	P<0.0001
Treatment	0.0053	**	Yes	F (3, 20) = 5.743	P=0.0053
Subject	<0.0001	****	Yes	F (20, 300) = 13.26	P<0.0001

Table 1. Two-Way Repeated Measures (RM) ANOVA summaries with significance for proportional commission error (top) and pooled efficiency metric (bottom).

Discussion

Long-term effects of cannabinoid administration during adolescence remain poorly understood. (24) This study explores two hypotheses pertaining to adolescent mice treated with WIN55,212-2 during adolescence. The first component used the Chronic Social Defeat Stress model to determine whether adolescent cannabinoid exposure altered susceptibility to stress as adults. The second considered alterations in impulsive behaviour in these animals as adults using the Go/No-Go operant conditioning task. By identifying behavioural correlates of exogenous modulation of the endocannabinoid system during a critical period of development, we may begin to ask more refined questions to identify underlying mechanisms of such alterations.

Since there were only 10 subjects in each treatment group exposed to CSDS, we cannot suggest an increase in susceptibility to stress as adults

in animals exposed to WIN during adolescence. The CSDS model is a validated and reliable method to produce stress-related phenotypes in wild-type mice. (30,32) With less than 10 animals in most treatment groups, a susceptibility rate of approximately 75% was globally observed. Despite finding no significant differences in susceptibility to stress which may indicate lack of effect, we cannot conclude that adolescent cannabinoid exposure does not change susceptibility to stress in adulthood. Notably, chronic low-doses of THC in adolescent but not adult rodents have been shown to produce depressive-like phenotypes. (36) There is compelling evidence, however, that WIN-treated animals showed greater levels of behavioural inhibition, as they demonstrated decreased impulsivity on the Go/No-Go task. High dose (WIN 2 mg/kg, 4 mg/kg) subjects learned to suppress previously conditioned behaviours remarkably quickly in comparison to both vehicle and low dose (WIN 0.5 mg/kg) animals in our sample. An alternative consideration is that the vehicle group in the study was particularly slow in this task. These findings diverge from what was previously identified in acute WIN and THC exposure, as well as adolescent WIN exposure. Neither chronic nor acute exposure to WIN have been shown to change impulsivity in rodents. (24,25) The endocannabinoid system contributes to the maturation of the prefrontal cortex; its modulation during adolescence has consequences that persist later in life. Future studies should aim to replicate these results and subsequently investigate underlying mechanisms associated with changes in impulsivity. Approaches such as stereology may be used to quantify morphological changes in dendritic architecture in regions of the prefrontal cortex, and functional calcium imaging studies may glean information on aberrant processing in this region.

The strength of this study is also its greatest limitation. By taking a broad scope and simultaneously investigating two separate lines of inquiry, simplicity in design as well as sample sizes were lost. These limitations need to be considered in the conclusions that can be drawn from either component of the study. Although this study may suggest that adolescent exposure to WIN does not alter susceptibility to stress, determining susceptibility to social defeat stress requires samples much larger than 10 per group for high sensitivity, particularly if susceptibility is not substantially altered. Upon replication of this study, changes to the experimental design should be considered, such as the use of two treatment groups and conducting a power calculation for sample sizes to detect changes in susceptibility with sufficient confidence and effect size. The consideration of sample size with the Go/No-Go task may be less problematic given that the variability for most groups is low. The more pertinent limitation on this behavioural task is the fact that animals were singly housed for approximately 3 weeks before Go/No-Go began. Social isolation is a known stressor for mice and may have posed an interaction effect with the behaviour we are interested in. (37,38) Finally, when comparing the vehicle controls in the study with controls from other studies, they appear to learn at a relatively slower rate. This may explain the astonishing comparisons drawn; replication studies are duly needed. Despite these limitations, the dose response effect of the drug is hard to ignore and warrants further investigation.

This finding contributes to the body of literature examining cognitive alterations in adulthood in response to early exposure to cannabinoids. These behavioural findings are novel and warrant further exploration of its validity and mechanisms. It would be quite interesting to repeat this experiment with THC for comparison and ecological validity. This would allow for mechanistic comparison of the effect of these drugs and reflect consumption of cannabis in a more accurate way. Reflecting on what Go/No-Go measures and the circuits associated with behavioural inhibition, it is worth considering the best approach to identifying the locus of initiating a go vs no-go response. (39) Perhaps an in-vivo experimental approach, such as calcium imaging or neural telemetry may be apt for characterising the cortical organisation which gives rise to this inhibitory behaviour, in addition to its alterations from cannabinoid exposure.

In summary, this study provides preliminary evidence for a dose-dependent increase in behavioural inhibition as measured by the Go/No-Go task in adult animals treated in adolescence with WIN. There were some key limitations in the study design and small sample sizes. We did not find evidence of altered susceptibility to stress in these animals. However, we report a decrease in impulsive behaviour in adolescent WIN-treated adults. Further studies and replication are needed to make meaningful conclusions. Research on the effects of cannabinoids in adolescence is especially important given its prevalence in society and association with mental health issues. Deepening our understanding of how drugs affect the developing brain is imperative in a time when evidence-based information on youth cannabis use is incomplete.

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