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Smoked Cannabis Effects in Cannabis Users at Clinical High-Risk for Psychosis: A Further Investigation of Cognition and Reward

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ABSTRACT

Objective. Some adverse cannabis effects are greater in individuals on the psychosis spectrum compared to healthy individuals. We have previously reported that smoked cannabis acutely worsened psychotic-like states and reduced cognitive performance selectively in cannabis users at clinical high-risk (CHR) for psychosis. The objective of the present study was to further investigate the acute effects of cannabis on cognition and reward processing in CHR cannabis users. **Method**. Six CHR cannabis users and six psychiatrically-healthy cannabis users comparable in intellectual, demographic, and cannabis use characteristics (including nontreatment-seeking status), participated in the study. Objective and subjective measures of cognition and cannabis reward, were completed before and after smoking half of an active (5.5% Δ^9tetrahydrocannabinol [Δ^9-THC]) or half of a placebo (0.0% Δ^9-THC) cannabis cigarette, under randomized/double-blind conditions. Repeated measures ANOVA tested main effects of drug condition (active vs. placebo) and/or the drug condition × time (baseline vs. post-administration) interactions; groups were analyzed separately due to the small sample size. **Results**. CHR participants exhibited evidence of decreased objective response inhibition and aversive intoxication following active cannabis, relative to placebo. Psychomotor speed and cannabis-related attentional bias were also affected by cannabis intoxication. No such effects were observed in psychiatrically-healthy cannabis users. **Conclusion**. These findings provide further preliminary evidence of a deleterious cognitive and reward-related response to cannabis in individuals with preexisting risk for psychosis.

Key words: marijuana; THC; cognition; prodromal psychosis; response inhibition

Cognitive functioning is an area of concern for individuals who use cannabis regularly (Crane et al., 2013). Cannabis with proportionally higher Δ9-tetrahydrocannabinol (Δ^9-THC) cannabinoid content may produce a wide range of acute cognitive effects in cannabis users, including temporary decreases in attention and working memory (Crane et al., 2013; Bhattacharyya et al., 2015), reduced inhibitory control and slowed decision-making (Oomen et al., 2018; Vadhan et al., 2007), and other related executive impairments (Cohen & Weinstein, 2018). However, these effects are not universal due to participant moderating factors, such as varying

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cannabis use histories and tolerance (Nordstrom & Hart, 2006; Ramaekers et al., 2016) and vulnerability to psychosis (Vadhan et al., 2017).

Cognitive functioning is also an area of concern for individuals across the psychosis spectrum in general (Bora et al., 2014; Thai et al., 2019), and cannabis use is common among these individuals (Myles et al., 2016). A recent review found that nearly half of all individuals at clinical high-risk for psychosis (CHR) reported using cannabis at some point in their life, and a quarter reported current cannabis use (Farris et al., 2020). Disturbances in response inhibition and working memory, which can be also produced by acute Δ^9-THC administration, are characteristic of psychosis-spectrum disorders (Ethridge et al., 2014). Additionally, the endocannabinoid system has been implicated in the pathophysiology of these disorders (Ferretjans et al., 2012; Murray et al., 2017), with findings of increased CB_1 receptor binding density and anandamide levels in cerebrospinal fluid (Leweke et al., 2018; Minichino et al., 2019).

Cannabis users with a psychotic disorder (e.g. schizophrenia) may exhibit comparable or even enhanced cognition when not intoxicated, relative to non-cannabis users with a psychotic disorder (e.g., Menendez-Miranda et al., 2019). However, when cannabis or Δ^9-THC has been directly administered to samples of cannabis users across the broad psychosis spectrum, a variety of adverse cognitive and behavioral effects have been observed. These effects include worsening of psychotic states and memory function (Sherif et al., 2016), and are of greater magnitude than those observed in cannabis users who are not on the psychosis spectrum (Mason et al., 2009; Vadhan et al., 2019); these differential effects may be additionally moderated by genetic factors (Di Forti et al., 2012). Moreover, under conditions of non-intoxication, the learning and attentional performance of cannabis users who report psychotic-like states after naturalistic cannabis use, have been shown to be poorer than cannabis users who report primarily euphoric states (Barkus et al., 2016).

Consistent with these findings, we found that administration of active smoked cannabis (5.5% Δ^9-THC) relative to placebo smoked cannabis (0.0% Δ^9-THC) increased subjective psychotic-like states (e.g., paranoia) and cognitive/perceptual disturbances (e.g., inattention, slowed time perception), while slowing logical reasoning (i.e., A Not B task) and reducing attentional control (i.e., Stroop), in cannabis users at clinical high-risk (CHR) for psychosis (Vadhan et al., 2017). No such effects were observed in psychiatrically-healthy cannabis users, although active cannabis increased heart rate and subjective intoxication in both groups.

Given the burgeoning evidence of a distinct and adverse acute response to cannabis in CHR individuals (Vadhan et al., 2019) that ordinarily should lead to cannabis cessation (Sami et al., 2019), open questions remain regarding the reasons such individuals use cannabis (which they may do at disproportionate rates). The endocannabinoid system interacts with other neurotransmitter systems (i.e., dopaminergic) for reward processing functions (Solinas et al., 2008). Thus, it is possible that anhedonia (i.e., difficulty in experiencing pleasure), a prominent symptom in CHR individuals (Cressman et al., 2015), may motivate cannabis use (Gill et al., 2015; Fischer et al., 2014), but also diminish its acute rewarding effects. Fischer et al. (2014) found that both smoked cannabis (3.6% Δ^9-THC) and oral administration of Δ^9-THC (15 mg capsules) increased connectivity between the nucleus accumbens and prefrontal cortical brain regions in cannabis users with schizophrenia, who showed impaired brain reward circuitry at baseline relative to healthy controls, supporting a hedonic role for cannabis in psychosis.

Further, cognitive deficits may increase vulnerability to initiation and maintenance of cannabis use (Li et al., 2020), and be negatively impacted by further cannabis use as well. Thus, further examination of acute cannabis effects on cognition, euphoria and reward processing in CHR individuals is warranted (Lawn et al., 2016; Vadhan et al., 2009), in line with calls for more experimental research in this area (Ksir & Hart, 2016). A better understanding of how CHR individuals respond to cannabis may have important implications for reducing risk of psychosis in vulnerable individuals.

Thus, this report further characterizes the acute effects of active cannabis (compared to placebo) on cognitive, as well as reward and related measures, in CHR and control cannabis users. We hypothesized that active (relative to placebo) would produce: 1) deleterious changes in objective and subjective cognition (i.e., decreased

response inhibition, working memory, and alertness), but 2) attenuated subjective rewarding effects, in the CHR but not the control group.

METHODS[1]

Participants

Participants were 12 non-treatment-seeking, adult regular cannabis users. Six were at clinical high-risk (CHR) for psychosis, and six were not (see ascertainment details below). All participants were physically and neurologically healthy (as assessed by a physician exam), and had an estimated intelligence quotient (IQ) >80. All participants were required to be young adults (aged 18-30), and must have reported weekly cannabis use for at least one month and regular cannabis use within the 6-month period before enrollment. Current cannabis use was verified by positive urine toxicology tests for Δ^9-THC metabolites on two different days.

All participants were administered the Structured Interview/Schedule of Psychosis Risk Symptoms Version 4.0 (SIPS/SOPS; McGlashan et al., 2001), which assesses the presence of 3 clinical high-risk syndromes (described below). All participants were also administered the Structured Clinical Interview for DSM-IV Axis I Disorders – Patient Edition (SCID-I/P; First et al., 1995), except for the psychotic disorders module, to assess for the presence of DSM-IV psychiatric disorders. Participants could not: 1) be seeking treatment for cannabis use; 2) have had a prior serious adverse reaction to cannabis (assessed by self-report); 3) meet DSM-IV criteria (assessed by the SCID-I/P) for any substance dependence, aside from cannabis dependence; 4) have a personal history of a psychotic or bipolar disorder; or 5) be on any psychoactive medication other than antidepressants. Antidepressant use was permitted given its prevalence in the CHR population (Goines et al., 2019; McGuire et al., 2011) and the corresponding difficulty in recruiting such individuals without such use. Two out of 6 CHR participants (but no control participants) were receiving antidepressants at the time of the study (the regimens were stable prior to and during participation). Additionally, female participants could not be pregnant (confirmed by a negative urine pregnancy test at each laboratory visit).

CHR participants were required to meet criteria for a clinical high-risk syndrome, with psychosis-risk symptoms not occurring exclusively in the context of cannabis use, as assessed by the SIPS/SOPS. Attenuated Positive Symptom Syndrome (APSS) is characterized by recent attenuated positive symptoms (e.g., suspiciousness, grandiosity) occurring at a subthreshold level of intensity; to meet criteria for APSS, a patient must have received a rating ≥ 3 on scales P1-P5 of the SOPS. Brief Intermittent Psychotic Syndrome (BIPS) is characterized by psychotic symptoms that are recent (began in the past three months) and fleeting in duration; to meet criteria for BIPS, a patient must have received a SOPS score = 6, and begun experiencing psychosis symptoms within the previous 3 months, for several minutes per day, at least once per month. Genetic Risk and Deterioration Syndrome (GRDS) is characterized by the presence of a psychotic disorder in a first-degree relative, with accompanying recent functional decline in the patient; to meet criteria for recent functional deterioration, a patient must have shown a decrease in Global Assessment of Functioning (GAF) score during the last month relative to his or her highest GAF score in the previous 12 months. In this study, all CHR participants met criteria for APSS.

Controls could not meet criteria for any of these CHR syndromes or possess first-degree familial risk for a psychotic disorder (SIPS/SOPS), nor for a current or lifetime history of a DSM-IV psychiatric disorder (SCID-I/P).

This study was approved by the Institutional Review Board at the New York State Psychiatric Institute. All data reported in this manuscript were obtained in compliance with regulations of the New York State Psychiatric Institute and the New York State Office of Mental Health, and all participants provided written informed consent.

Recruitment

CHR participants were primarily recruited from the Center for Prevention and Evaluation (COPE), an outpatient research program at the New York State Psychiatric Institute (NYSPI) for

[1]Additional methodological detail can be found in the online supplement.

CHR patients. Control participants were primarily recruited via newspaper advertisement and word-of-mouth referral in New York City. Secondary recruitment from the NYSPI Substance Use Research Center (SURC) Outpatient Cannabis Laboratory also occurred (potential CHR participants were identified with a screening instrument [Miller et al., 2004] and then received formal ascertainment [SIPS/SOPS]).

Demographic, Clinical and Substance Use Characteristics

CHR participants were 23.2 (SD=4.0) years of age, had 14.4 (SD=1.7) years of formal education, a mean estimated Full Scale IQ (FSIQ) of 105.7 (SD=10.9), and consisted of 5 males (3 Hispanic, 1 African-American, 1 Caucasian) and 1 female (Hispanic). Similarly, control participants were 24.3 (SD=3.0) years of age, had 13.5 years (SD=2.7) of formal education, an estimated FSIQ of 102.2 (SD=13.9), and consisted of 4 males (2 Hispanic, 1 African American, 1 Asian- American) and 2 females (1 Hispanic and 1 mixed Hispanic/African American). The groups did not differ statistically on any of these characteristics ($p > 0.05$).

CHR and control participants were also comparable on substance use characteristics ($p > 0.05$; see Table S1), including age of onset of cannabis use (~16 years on average for both groups), frequency of cannabis use (~4 times per week on average for both groups), and frequency of alcohol use (~2 times per week on average for both groups). Other than occasional hallucinogen/stimulant use by two CHR participants, no one in either group reported current use of other illicit substances, which was verified by urine toxicology tests.

The CHR participants exhibited greater levels of psychopathology relative to controls (Table S1; $p < 0.05$), including anxiety disorders (n=4 vs n=0), mood disorders (n=2 vs n=0), and symptoms of psychosis-risk (SOPS), depression (Beck Depression Inventory – Second Edition; BDI-II; Beck et al., 1996) and anxiety (Beck Anxiety Inventory; BAI; Beck et al., 1988), but not anhedonia ($p > 0.05$; Chapman Anhedonia - Revised Scales; Chapman et al., 1976). The CHR group also endorsed greater levels of expectancy of negative cannabis effects than the control group ($p < 0.05$; Marijuana Effect Expectancy Questionnaire; Schäfer & Brown, 1991).

Cannabis Administration Sessions

Participants were scheduled to attend 3 separate laboratory sessions (scheduled at least 72 hours apart), during which they smoked half of a cannabis cigarette containing 0.0%, 2.02%, or 5.05% Δ^9-THC (all containing 0.01% cannabidiol [CBD]), in a randomized and double-blinded fashion. Cannabis cigarettes were provided by the National Institute on Drug Abuse (NIDA) and smoked according to a standardized paced-puffing procedure (see S1.1).

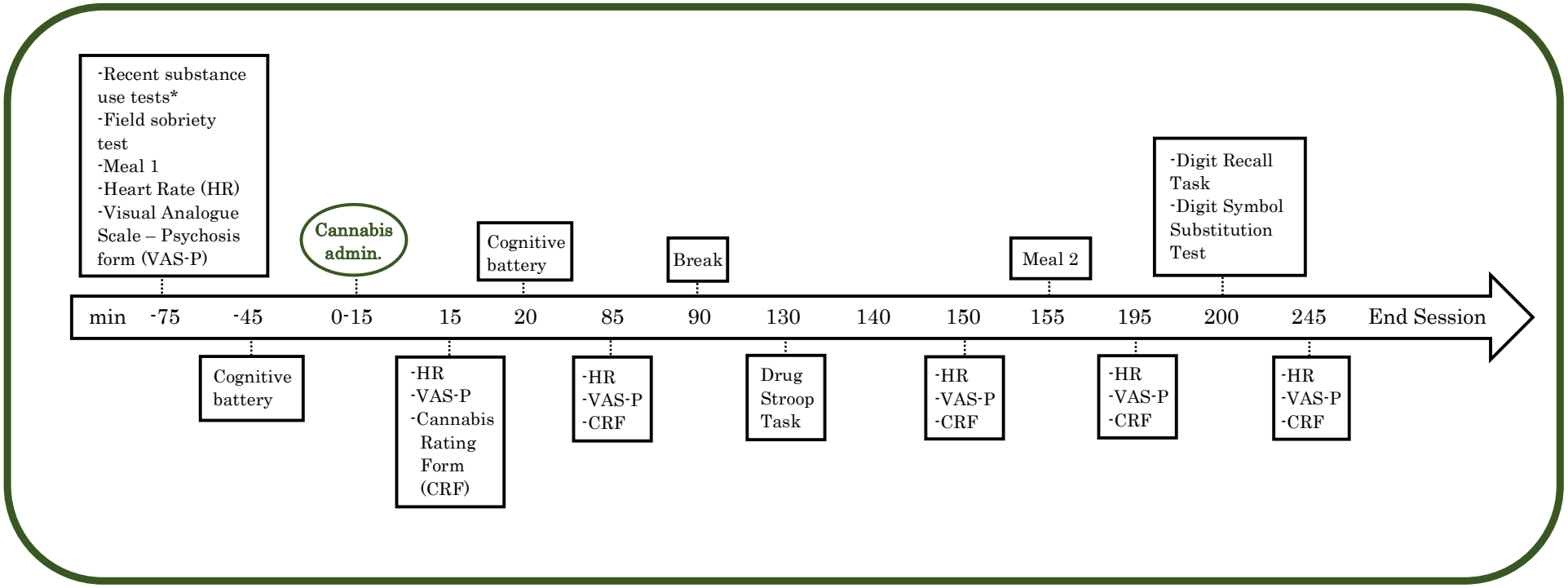
All participants completed the 0.0% and 5.05% Δ^9-THC sessions; however, 2 CHR participants were unable to attend their 2.02% Δ^9-THC sessions. Thus, only data from the 0.0% and 5.05% Δ^9-THC sessions were formally analyzed and reported here.

See Figure 1 for the session timeline. All participants were required to abstain from using cannabis on the morning of each session, as well as any other psychoactive drugs, with the exception of usual caffeine and prescribed medication (for CHR participants). Compliance was confirmed via self-report and CO^2 breath tests. Additionally, field sobriety tests were administered before cannabis administration; no participant was found to be intoxicated before any of the laboratory sessions. Two meals were served during each laboratory session. After the first meal, participants completed the primary cognitive battery and subjective measures (see below), and consumed the second meal approximately 2.5 hrs post-active or –placebo cannabis administration.

Objective Measures

Participants completed the computerized cognitive battery in the 45 min period before cannabis administration and repeated the battery in the 20-80 min period after smoking. The primary measures were the GNG and N-Back tasks. The secondary measures were the Digit Recall task (DRT) and Digit Symbol Substitution Test (DSST) (additionally administered approximately 3 hrs post-administration) and the Drug Stroop (Carpenter et al., 2006) task (administered at 130 min post-administration).

Figure 1. *Session Timeline*



*Urine toxicology, breath-CO and -alcohol tests, and a recent substance use questionnaire.

The N-Back task (Cohen et al., 1997; Keilp et al., 2014) assessed visual working memory though a continuous-recognition task where numeric stimuli that appeared 2 trials (2-Back condition) and 3 trials back (3-Back) were identified. d' scores were computed for an aggregate summary score of total hit rate, false alarms (i.e., incorrect matches), and random responses. The Go/No-Go task (GNG; abbreviated version, Keilp et al., 2014) assessed response inhibition by measuring identification of a specific combination of visual and auditory stimuli. The total number of incorrect responses (i.e., commission errors) was examined. The Digit Recall Task (DRT; Hart et al., 2001) assessed immediate visual memory through a task where numeric stimuli (i.e., 8-digit number strings) were reproduced both while and immediately after they appeared on the computer screen. The total number of correctly copied number strings (before recall) and percent correctly reproduced during immediate recall were examined. The Digit Symbol Substitution Test (DSST; computerized version, McLeod et al., 1982) assessed psychomotor speed though a procedure in which geometric stimuli associated with different numbers were reproduced under timed conditions. The total percent correct was examined. The Drug Stroop Task (Carpenter et al., 2006) assessed drug-related attentional bias by measuring reaction time to name the font color of drug-related and neutral words. Interference from cannabis-related words and from mixed drug words were examined.

For more detailed descriptions of these cognitive measures see S1.3.

Subjective Measures

Participants completed a computerized and modified Visual Analogue Scale (VAS- P; Vadhan et al., 2017) pre- and post-cannabis administration at 5 timepoints (15-, 85-, 150-, 195-, and 245-min); see Table S4. The primary measures were "I feel a *Good Drug effect*", "I feel a *Bad Drug effect*", "I feel *Alert*", and, I feel *Sleepy*". The secondary measure was a computerized Cannabis Rating Form (CRF; Haney et al., 2016), given only post-administration at 5 timepoints (15-, 85-, 150-, 195-, and 245-min); "*Strength*" and "Desire to *Take Again*" were examined here. Both measures consisted of items for rating displayed one at a time below a 100-mm line, with anchors of "Not at all" and "Extremely."

Statistical Analyses

A similar analytic approach as the previous article from this study (Vadhan et al., 2017) was employed. Smoking topography and acute cannabis effects were assessed for each group independently given the small sample size. Within-participant repeated measures ANOVA examined the main effects of drug condition (active [5.50% Δ^9-THC] vs. placebo) and/or the interactions between drug condition and time (baseline vs. post-administration) on most dependent measures, with simple effects tests (comparing active vs. placebo at each timepoint) to probe significant interactions. This approach demonstrated adequate power (Kyonka, 2019; see S1.4.1). Statistical significance thresholds for ANOVAs varied from α=0.013 to 0.05 based on the magnitude of correction required for family-wise error rate (see S1.4.2), and missing data procedures are described in S1.4.3. Questionnaire measures were compared directly between groups with independent sample t-tests with α= 0.05.

RESULTS

All main effects of drug condition and drug condition × time interactions are described below (including statistical results for significant and matching nonsignificant tests); raw data and all F-test results can be found in supplemental tables as indicated.

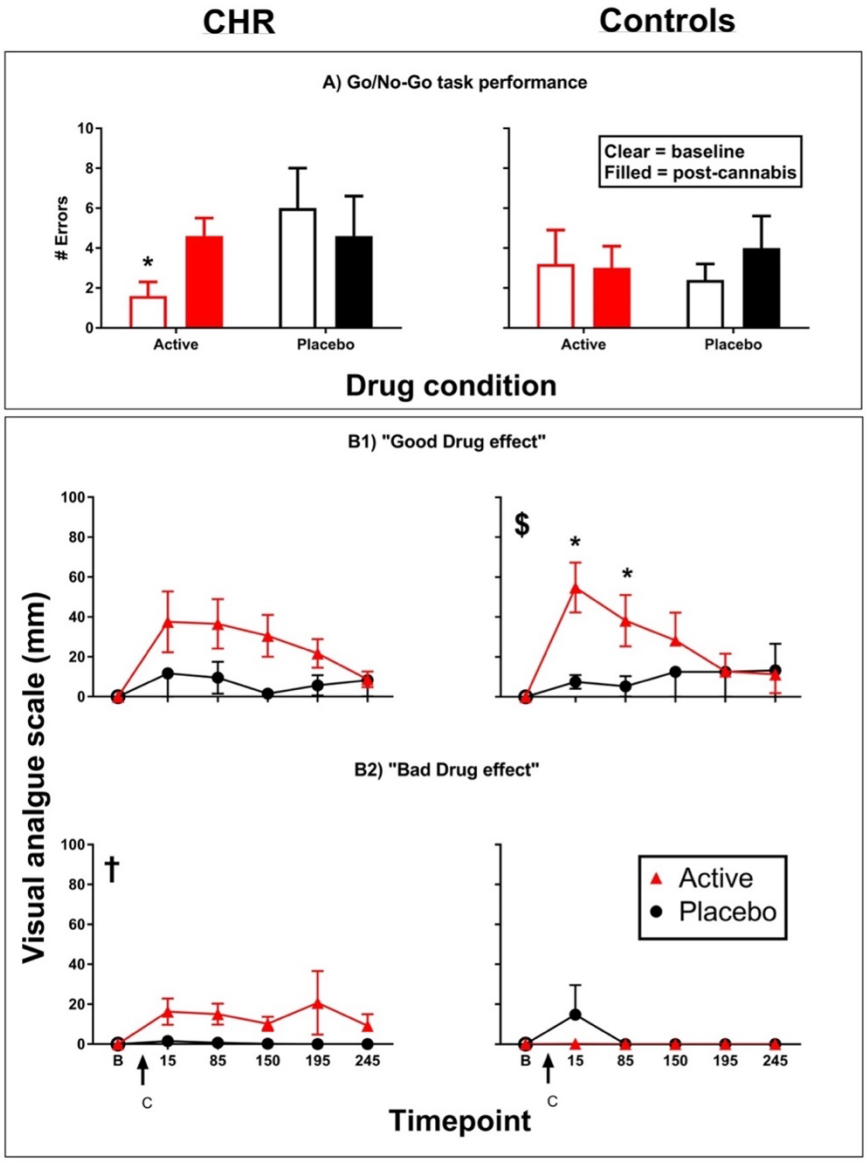
There were no main effects of drug condition for the number of puffs inhaled for either the CHR (4.0 [SD=0.4] vs. 3.5 [SD=0.2] puffs [active vs. placebo cannabis]; F = 1.4(1,5), p = 0.30, $\eta p2$ = 0.21) or control group (4.7 [SD=0.3] vs. 4.2 [SD=0.3] puffs [active vs. placebo cannabis]; F = 1.4(1,5), p = 0.30, η p2 = 0.21).

Go/No-Go task (Figure 2A). On number of commission errors, there was no main effect of drug condition for either group (p > 0.025). However, for the CHR group, there was a significant drug condition × time interaction (F = 16.7(1,4), p < 0.025, $\eta p2$ = 0.81), with a decreased number of commission errors at baseline relative to placebo under active cannabis (p < 0.05), but no differences between drug conditions at post-administration (p > 0.05). No drug condition ×

time interaction was observed for the control group (F = 1.5(1,4), $p > 0.025$, ηp2 = 0.28).

For rewarding intoxication ("I feel a Good Drug effect"; Figure 2B1), there were no main effects of drug condition for either group ($p > 0.013$). However, there was a drug condition × time interaction for the control group ($F = 3.8(5,25)$, $p < 0.013$, ηp2 = 0.43), but not the CHR group ($F = 2.0(2.0,10.2)$, $p > 0.013$, ηp2 = 0.28). The control group reported an increased good drug effect following active cannabis administration, relative to placebo. For aversive intoxication ("I feel a Bad Drug effect"; Figure 2B2), there was a main effect of drug condition for the CHR group ($F = 14.0(1,5)$, $p < 0.013$, ηp2 = 0.74), but not the control group ($F = 1.0(1,5)$, $p > 0.013$, ηp2 = 0.16). The CHR group reported an increased bad drug effect during the active cannabis condition relative to placebo.

Figure 2. *Go/No-Go performance (A) and subjective Good (B1) and Bad (B2) Drug Effect before and after cannabis administration as a function of group (Clinical High-Risk [CHR], left side; Controls, right side).*



Note. Error bars reflect SEM. †main effect of drug condition; $drug condition × time interaction. *active (5.5% Δ^9-THC) differs from placebo (0.0% Δ^9-THC); $p < 0.025$ (Go/No Go) and $p < 0.013$ ("Good/Bad Drug Effect"); Full ANOVA results in Tables S2 and S4.

For *N-Back task* d' scores there was no main effect of drug condition, nor any drug condition × time interaction, for either group ($p > 0.025$; Table S2). For *Digit-Recall Task (DRT)* number correct, there was a main effect of drug condition for the CHR group ($F = 32.7(1,4)$, $p < 0.013$, $\eta p2 = 0.89$), but not the control group ($F = 0.0(1,5)$, $p > 0.017$, $\eta p2 = 0.01$). CHR participants copied fewer number strings correctly under the active cannabis condition relative to placebo (Table S2A). No drug condition × time interaction was found for either group ($p > 0.017$).

On *DRT* percent immediate recall, there was no main effect of drug condition nor a drug condition × time interaction for either group ($p > 0.017$).

For *Digit Symbol Substitution Test* total percent correct, there was no main effect, nor a drug condition × time interaction for either group ($p > 0.017$).

For *Drug Stroop Task (Table S3)* interference reaction time, there was no main effect of drug condition, nor a main effect of word type for either group ($p > 0.05$). However, there was a drug condition × word type interaction for the CHR group ($F = 7.9(1,4)$, $p < 0.05$, $\eta p2 = 0.67$). CHR participants exhibited decreased interference from cannabis-related words (relative to mixed drug-related words), under the active cannabis condition. No drug condition × word type interaction was observed for the control group ($F = 0.1(1,5)$, $p > 0.05$, $\eta p2 = 0.01$).

For sleepiness and alertness ("I feel *Sleepy*", "I feel "Alert"), there were no main effects of drug condition, nor any drug condition × time interactions, for either group ($p > 0.013$). For perceived cannabis potency ("*Strength*"), there were main effects of drug condition for both the CHR ($F = 10.8(1,5)$, $p < 0.025$, $\eta p2 = 0.68$) and control groups ($F = 19.0(1,5)$, $p < 0.025$, $\eta p2 = 0.79$), with both groups reporting increased cannabis strength for the active cannabis condition (relative to placebo). There was no drug condition × time interaction for either group ($p > 0.025$). There was no main effect of drug condition, nor any drug condition × time interaction, for "Desire to Take Again" ($p > 0.025$; Table S4).

DISCUSSION

Smoked active cannabis (5.5% Δ^9-THC), relative to placebo (0.0% Δ^9-THC), decreased objective response inhibition, and increased subjective aversive intoxication in cannabis users at clinical high-risk for psychosis (CHR). Additionally, psychomotor speed and cannabis-related interference on a measure of attentional bias (Drug Stroop) were reduced under the active cannabis condition (relative to placebo). In contrast, control participants exhibited no objective cognitive alterations, and increased rewarding intoxication, under the active cannabis condition (relative to placebo). These data are partially consistent with our hypotheses.

Disruptions in working memory, response inhibition, attention, and psychomotor speed are hallmark features of psychotic disorders (Mihaljević-Peleš et al., 2019) and their risk syndromes (Mourik et al., 2017). These disruptions can also be acutely produced by cannabis intoxication in individuals with current or past cannabis use (Ramaekers et al., 2016; Vadhan et al., 2009). However, although the groups in the current study were not compared directly, the results may suggest a preferential acute deleterious effect of cannabis on these and related functions in CHR cannabis users.

Different effects were also seen for the reward-related measures, with a global negative effect for active cannabis emerging for the CHR group (though the nonsignificant positive effect was about twice the size), and a global positive effect for the control group. These findings are consistent with the pattern of cognitive and psychiatric effects reported here and previously (Vadhan et al., 2017), as well as with the groups' preexisting expectations (MEEQ). These participant-predicted and experimenter-observed aversive effects in the CHR group, as well as the lack of group differences on anhedonia symptoms, deepen the question of their reasons for regular cannabis use (Di Forti et al., 2007). Speculatively, the change in Drug Stroop task performance under the active cannabis condition – an apparent shift in cannabis-stimuli-related attentional bias from interference to facilitation – may reflect an appetitive process related to cannabis intoxication. It is also possible that CHR cannabis users, who show similar abnormalities in brain function to cannabis users with schizophrenia (Millman et al., 2019), may also exhibit similar Δ^9-THC–induced changes in brain reward system functioning (e.g., Fischer et al., 2014; Whitfield-Gabrieli et al., 2018).

In sum, these data indicate that cognitive impairment and an aversive drug state were increased during cannabis intoxication in CHR but not healthy cannabis users, providing further preliminary evidence of a distinct and adverse response to cannabis in individuals with preexisting risk for psychosis. The primary methodological limitation is the small sample size, which is likely responsible for the high baseline performance variability (e.g., GNG errors), only some effects reaching statistical significance, and our inability to statistically account for antidepressant use in the CHR group. However, the small sample should not necessarily contribute to a preferential effect for the CHR individuals, and correction for multiple comparisons was employed.

It is interesting that these CHR individuals with extensive cannabis experience do not appear tolerant to the observed adverse effects in the manner that the psychiatrically healthy cannabis users with similar experience appear to be (also see Schwope et al., 2012). This leads us to conclude that the risk for psychosis, including its accompanying psychiatric symptoms, may play a role in these differing effects. While increasing evidence does indicate that cannabis differentially impacts individuals on the broad psychosis spectrum (Vadhan et al., 2019), research with methodological improvements such as larger sample sizes and mixed within- and between-group analyses is needed to confirm and expand on these results.

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