Supplementary Materials for:

Smoked cannabis effects in cannabis users at clinical high-risk for psychosis: A further investigation of cognition and reward

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1. **Method**[**1**](#_bookmark0)
   1. **Cannabis administration sessions.**

For the paced puffing procedure (Haney et al., 2016), participants were instructed to: 1) light the cigarette (30 sec), 2) prepare (5 sec), 3) inhale (5 sec), 4) hold the smoke in their lungs (10 sec), and 5) exhale. They smoked one puff every minute with a 40-s interval between each puff, until they had smoked 50% of the cigarette.

* 1. **Safety and follow-up procedures.**

Participants had to agree not to drive to and from sessions and were provided with public transportation or taxi fare. All participants equaled or surpassed their baseline field sobriety tests (FST) performance after each session. Psychiatric staff were readily available during all CHR sessions, and CHR participants were required to pass a brief psychiatric exam before leaving. Study debriefing, 3-4 clinical follow-up, and motivational interviewing (Miller & Rollnick, 2002) sessions (CHR group only), were scheduled following the last session.

* 1. **Objective measures.**

*N-Back task* (Cohen, et al., 1997; Keilp et al., 2014). On this visual working memory task, a series of numbers flashed one at a time on the computer screen (e.g., 5, 2, 8), and participants were prompted to press the response key when the number on the screen had appeared 2 times back. Following this 2-back condition, a 3-back version was administered, during which participants were prompted to respond only when the number on the screen appeared 3 trials back. Standard versions of the 2- and 3-back tasks were used, containing 60 trials each; 2 different stimulus orders were employed in a counterbalanced fashion (versions A and B).

[[1]](#footnote-1)

*Go/No-Go task* (GNG; Keilp et al., 2014). On this measure of response inhibition, an X appeared for 50 ms once per s in one of six locations on a computer screen. Participants were instructed to press the response key only when the X appeared in the top half of the screen with an accompanying low tone (200 Hz), as opposed to a high tone (400 Hz). The presentation of stimuli was randomized with each administration. An abbreviated version containing 1/3 the number of trials (tot = 75) was employed, which has shown good reliabilityand validity (data available upon request).

*Digit-Recall Task* (DRT; Hart et al., 2001). On this task of immediate and delayed recall, 8-digit number strings appeared on the computer screen, one at a time (e.g., 19293257), and participants were instructed to reproduce each number string immediately when it was still displayed on the screen, and again when it disappeared. Each participant was given 3 m to complete as many number strings as possible.

*Digit Symbol Substitution Test* (DSST; McLeod et al., 1982).On this measure of processing speed, a total of 9 arrangements of 3 by 3 hyphens were displayed at the top of the computer screen. For each arrangement, 3 hyphens were replaced with 3 dark asterisks to create a unique geometric configuration, and each arrangement had a corresponding number 1-9. For example, in the first arrangement, the asterisk was located on the top right of the first row, on the center of the second row, and on the center of the third row; in the second arrangement, the asterisk was located in the center of the top row, on the right of the second row, and in the middle of the third row. In the center of the computer screen, below these 9 geometric configurations, 1 of the 9 numbers appeared. Participants used a 3 by 3 keypad to reproduce the corresponding pattern of asterisks and were given 30 s to reproduce the patterns associated with 6 randomly generated numbers.

*Drug Stroop Task* (Carpenter et al., 2006). On this measure of drug-related attentional bias, 100 words appeared on the computer screen, one at a time (two blocks of 50 trials) in red, blue, green, or yellow ink. The words were either drug-related (i.e., cannabis, heroin, cocaine, or mixed) or neutral (e.g., lamp). Participants were asked to respond as quickly and as accurately as possible to each word by pressing the same colored key on a response pad. Interference from cannabis-related words was computed by subtracting participants’ average response time to neutral words from their average response time to cannabis-related words (greater interference was indicated by greater values).

* 1. **Statistical analyses**

**1.4.1.** **Power.**

Two compromise power analyses (Kyonka et al., 2019) were conducted with G\*Power (Faul et al., 2007) to assess the ability of our design to detect condition × time interactions, with input parameters based on the results of Vadhan et al. (2017). These power calculations are appropriate for small-sample studies of rare clinical populations where the sample size is fixed (Kyonka, 2019). For the primary cognitive battery (2 × 2), to detect an effect size (f) of 1.60, with a β/α ratio of 1, power ranges from 0.87 (n=6) to 0.83 (n=5). For the primary subjective battery (2 × 6), to detect an effect size (f) of 1.03, with a β/α ratio of 1, power is 0.93 (n=6).

**1.4.2. Correction for family-wise (i.e., experiment-wide) error rate (FWER).**

For the acute behavioral effects of cannabis, experiment families (4 total) were created according to the measurement type (objective or subjective) and frequency (2, 3, 5 or 6 timepoints) ([Ludbrook, 1998](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3497551/#b5)). A corrected alpha was calculated for each family (0.05/#outcomes; Olejnik, 1997), and pairwise tests were only conducted and interpreted for those omnibus tests considered significant under the corrected alpha. Due to the preliminary nature of the study, and the possibility of increasing Type I error, pairwise comparisons were left uncorrected.

1) Cognitive

a. 2 timepoints (N-Back, GNG), corrected alpha: 0.05/2=0.025

b. 3 timepoints (DRT Copy, DRT Imm. Rec., DSST), corrected alpha: 0.05/3=0.017

2) Subjective

a. 5 timepoints (*“Strength”*, *“Desire to Take Again”*), corrected alpha: 0.05/2=0.025

b. 6 timepoints (“Good/Bad Drug Effect”, “Alert”, “Sleepy”), corrected alpha: 0.05/4=0.013

**1.4.3. Missing data.**

One CHR participant was unable to complete any objective measures during the active

cannabis condition, and one control participant had invalid GNG data that was not included in analyses; sample sizes for all measures are located in their respective tables. Missing

cognitive data (7%) were estimated with conservative procedures consisting of linear regression (Garson, 2014) or substitution of adjacent data where regression was not possible (see Vadhan et al., 2017).

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| Table S1. Demographic, Substance Use and Clinical Characteristics. | | | | | | |
|  | CHR (n=6) | | Controls (n=6) | | Test value | P value |
| Demographics | M | SD | M | SD |  |  |
| Age (years) | 23.2 | 4.0 | 24.3 | 13.5 | t(10) = 0.57 | 0.58 |
| Education (years) | 14.4 | 1.7 | 13.5 | 2.7 | t(10) = -0.68 | 0.51 |
| Cannabis use |  |  |  |  |  |  |
| Age of first use (years) | 15.8 | 3.0 | 16.5 | 3.0 | t(10) = 0.44 | 0.67 |
| DSM-IV Cannabis Use Disorder | n=5 |  | n=4 |  | Fisher’s exact = 1.0 | |
| Past 30 days |  |  |  |  |  |  |
| Frequency (days/week) | 4.1 | 2.0 | 4.2 | 1.4 | t(10) = 0.08 | 0.94 |
| Amount ($/week) | 39.2 | 32.0 | 47.5 | 50.8 | t(10) = 0.34 | 0.74 |
| Alcohol use |  |  |  |  |  |  |
| Frequency (days/week) | 1.6 | 0.9 | 1.9 | 0.9 | t(9) = 0.58 | 0.58 |
| Amount (SDUs/week) | 4.3 | 2.8 | 3.3 | 1.4 | t(7.5) = 0.80 | 0.45 |
| Schedule of Psychosis Risk Symptoms (SOPS) |  |  |  |  |  |  |
| **Positive Symptoms\*** | **12.0** | **4.4** | **0.8** | **0.8** | **t(5.3) = 6.2** | **0.001** |
| **Negative Symptoms\*** | **10.7** | **5.3** | **0.5** | **0.8** | **t(5.3) = 4.6** | **0.005** |
| **Disorganized Symptoms\*** | **8.0** | **3.2** | **0.3** | **0.5** | **t(5.3) = 5.9** | **0.002** |
| **Beck Depression Inventory - Second Edition (BDI-II)\*** | **9.7** | **4.0** | **0.2** | **0.4** | **t(5.1) = 5.8** | **0.002** |
| **Beck Anxiety Inventory (BAI)\*** | **12.2** | **8.4** | **0.0** | **0.0** | **t(5.0) = 3.5** | **0.02** |
| Marijuana Effect Expectancy Questionnaire Subscales |  |  |  |  |  |  |
| **Cognitive and Behavioral lmpairment\*** | **33.1** | **6.7** | **22.0** | **8.9** | **t(10) = -2.44** | **0.04** |
| Relaxation | 27.0 | 6.4 | 27.6 | 4.3 | t(10) = 0.18 | 0.86 |
| Social and Sexual Facilitation | 26.7 | 6.8 | 23.7 | 5.6 | t(10) = -0.83 | 0.43 |
| Perceptual and Cognitive Enhancement | 26.7 | 3.7 | 20.9 | 6.2 | t(10) = -1.95 | 0.08 |
| **Negative Effects\*** | **16.3** | **3.8** | **10.8** | **1.8** | **t(10) = -3.15** | **0.01** |
| Craving and Physical Effects  **Chapman Anhedonia – Revised Scales** | 24.0 | 1.9 | 22.8 | 3.4 | t(10) = -0.73 | 0.48 |
| Physical | 14.2 | 5.3 | 16.8 | 9.7 | t(10) = 0.59 | 0.57 |
| Social | 15.8 | 6.2 | 9.7 | 5.6 | t(10) = - 1.8 | 0.10 |
| \* indicates a significant group difference (*p* < 0.05). | | | | | | |

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| Table S2. Objective Cognitive Effects. | | | | | | | | | | | | | | |
|  | | Active cannabis | | | Placebo cannabis | | | ANOVA results | | | | | | |
| Timepoint | | B | T1 | T2 | B | T1 | T2 | n | Main effect of drug condition | | | Drug condition × time interaction | | |
| **A) CLINICAL**  **HIGH-RISK** |  |  |  |  |  |  |  |  | Test value | p | ηp2 | Test value | p | ηp2 |
| N-Back (d’) (n=5) | M | 2.6 | 2.3 | - | 2.4 | 2.6 | - | 5 | F(1,4) = 0.0 | 0.98 | 0.00 | F(1,4) = 0.4 | 0.17 | 0.80 |
| (α=0.025) | SEM | 0.3 | 0.5 | - | 0.4 | 0.4 | - |  |  |  |  |  |  |  |
| **GNG (err.) (n=5)** | **M** | **1.6\*** | **4.6** | **-** | **6.0** | **4.6** | **-** | **5** | F(1,4) = 1.0 | 0.38 | 0.20 | **F(1,4) = 16.7** | **0.02** | **0.81** |
| (α=0.025) | SEM | 0.7 | 0.9 | - | 2.0 | 2.0 | - |  |  |  |  |  |  |  |
| **DRT copy (# correct) (n=5)** | **M** | **7.2** | **7.4** | **7.8** | **7.8** | **8.0** | **8.0** | **5** | **F(1,4) = 32.7** | **0.01** | **0.89** | F(2,8) = 0.3 | 0.74 | 0.73 |
| (α=0.017) | SEM | 0.4 | 0.2 | 0.2 | 0.2 | 0.0 | 0.0 |  |  |  |  |  |  |  |
| DRT imm rec. (%)  (n=5) | M | 69.0 | 61.0 | 63.4 | 79.0 | 82.6 | 77.8 | 5 | F(1,4) = 3.0 | 0.16 | 0.43 | F(2,8) = 1.9 | 0.21 | 0.32 |
| (α=0.017) | SEM | 17.5 | 13.4 | 13.1 | 9.1 | 9.4 | 7.2 |  |  |  |  |  |  |  |
| DSST (% acc.)  (n=5) | M | 97.8 | 93.8 | 93.0 | 92.8 | 93.8 | 96.4 | 5 | F(1,4) = 0.5 | 0.13 | 0.74 | F(3,12) = 3.14 | 0.07 | 0.46 |
| (α=0.017) | SEM | 1.3 | 1.6 | 1.4 | 3.4 | 1.7 | 1.1 |  |  |  |  |  |  |  |
| **B) CONTROLS** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| N-Back (d’) (n=6) | M | 3.1 | 3.0 | - | 3.0 | 3.3 | - | 5 | F(1,4) = 0.1 | 0.80 | 0.02 | F(1,4) = 0.5 | 0.53 | 0.11 |
| (α=0.025) | SEM | 0.4 | 0.6 | - | 0.6 | 0.5 | - |  |  |  |  |  |  |  |
| GNG (err.) (n=5) | M | 3.2 | 3.0 | - | 2.4 | 4.0 | - | 5 | F(1,4) = 0.02 | 0.91 | 0.00 | F(1,4) = 1.5 | 0.29 | 0.28 |
| (α=0.025) | SEM | 1.7 | 1.1 | - | 0.8 | 1.6 | - |  |  |  |  |  |  |  |
| DRT copy (# correct) (n=6) | M | 6.5 | 6.0 | 6.6 | 6.2 | 6.3 | 6.5 | 6 | F(1,5) = 0.0 | 0.86 | 0.01 | F(2,10) = 1.0 | 0.40 | 0.17 |
| (α=0.017) | SEM | 2.0 | 2.8 | 1.8 | 2.2 | 1.9 | 1.8 |  |  |  |  |  |  |  |
| DRT imm rec. (%)  (n=6) | M | 74.0 | 78.2 | 70.0 | 80.5 | 75.0 | 72.3 | 6 | F(1,5) = 0.2 | 0.67 | 0.04 | F(2,10) = 0.2 | 0.80 | 0.05 |
| (α=0.017) | SEM | 9.3 | 10.3 | 8.6 | 10.7 | 9.5 | 11.4 |  |  |  |  |  |  |  |
| DSST (% acc.)  (n=6) | M | 96.0 | 95.8 | 94.7 | 95.4 | 95.7 | 97.1 | 6 | F(1,10) = 0.2 | 0.65 | 0.02 | F(3,30) = 1.1 | 0.37 | 0.10 |
| (α=0.017) | SEM | 1.6 | 1.0 | 1.0 | 1.7 | 1.0 | 0.9 |  |  |  |  |  |  |  |

M=mean; SEM=standard error of measurement; **Bold** indicates a significant main effect of drug condition or drug condition × time interaction according to the corrected alpha. For every significant interaction, a difference between active and placebo cannabis at specific timepoints is indicated by:\**p* < the corrected alpha. N-Back, d’ score; GNG (err.), Go/No-Go, total number of commission errors; DRT copy (#), Digit-Recall Task (number copied during immediate free-call); DRT imm rec. (%), Digit-Reca ll Task, immediate recall (percent correct); DSST (% acc), Digit-Symbol Substitution Test (percent accuracy); T2, second post-cannabis assessment (DRT and DSST only).

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| Table S3. Drug Stroop Task Performance. | | | | | | | | | | | |
|  | Interference RT (ms) | | ANOVA Results | | | | | | | | |
| Main effect of drug condition | | | Word Type | |  | Drug condition × Word  Type | | |
| Active  cannabis | Placebo  cannabis | Test value | p | ηp2 | Test value | p | ηp2 | Test value | p | ηp2 |
| **A) CLINICAL**  **HIGH-RISK (n=5)** |  |  |  |  |  |  |  |  |  |  |  |
| **Cannabis stimuli (mean, SEM)** | **-19.7 (47.5)** | **19.5 (9.2)** | F(1,4) =0.35 | 0.58 | 0.08 | F(1,4) = 1.7 | 0.26 | 0.30 | **F(1,4)=7.9** | **.048** | **0.67** |
| **Mixed stimuli, (mean, SEM)** | **-20.6 (56.4)** | **-6.7 (13.1)** |
| **B) CONTROLS (n=6)** |  |  |  |  |  |  |  |  |  |  |  |
| Cannabis stimuli, mean (SEM) | -7.7 (31.2) | -9.1 (17.1) |  |  |  |  |  |  |  |  |  |
| Mixed stimuli, mean (SEM) | 10.6 (20.8) | 3.2 (18.7) | F(1,5)= 0.04 | 0.86 | 0.01 | F(1,5) = 1.7 | 0.25 | 0.25 | F(1,5)=0.1 | 0.81 | 0.01 |
| RT=reaction time; SEM=standard error of measurement; **Bold** indicates a significant drug condition × word type interaction; *p* < 0.05. | | | | | | | | | | | |

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| Table S4. Subjective Effects. | | | | | | | | | | | | | | | | | | | | |
| Timepoint (min) | | Active cannabis | | | | | | Placebo cannabis | | | | | | ANOVA results | | | | | | |
| B | 15 | 85 | 150 | 195 | 245 | B | 15 | 85 | 150 | 195 | 245 | n | Main effect of drug  condition | | | Drug condition × time  interaction | | |
| **A) CLINICAL HIGH-**  **RISK (n=6)** | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| VAS-P (mm) |  |  |  |  |  |  |  |  |  |  |  |  |  |  | Test value | p | ηp2 | Test value | p | ηp2 |
| “I feel a *Good Drug effect*” | M | 0.0 | 37.5 | 36.5 | 30.5 | 21.7 | 8.7 | 0.0 | 11.7 | 9.5 | 1.5 | 5.7 | 8.3 | 6 | F(1,5)  = 3.1 | 0.14 | 0.38 | F(2.0,10.2)  = 2.0 | 0.19 | 0.28 |
| (α=0.013) | SEM | 0.0 | 15.3 | 14.9 | 10.5 | 7.2 | 4 | 0.0 | 11.7 | 8 | 1.5 | 5.1 | 8.2 |  |  |  |  |  |  |  |
| **“I feel a *Bad Drug effect*”** | **M** | **0.0** | **16.3** | **15.0** | **10.2** | **20.7** | **9.2** | **0.0** | **1.5** | **0.7** | **0.2** | **0.0** | **0.0** | 6 | **F(1,5)**  **= 14.0** | **0.01** | **0.74** | F(1.3,6.7)  = 0.8 | 0.44 | 0.14 |
| (α=0.013) | **SEM** | **0.0** | **2.6** | **6.1** | **4.2** | **8.4** | **3.8** | **0.0** | **0.6** | **0.3** | **0.1** | **0.0** | **0.0** |  |  |  |  |  |  |  |
| “I feel *Alert*” | M | 47.8 | 40.5 | 37.5 | 45.7 | 42.8 | 28.2 | 28.2 | 28.8 | 32.2 | 29.2 | 33.2 | 26.2 | 6 | F(1,5)= 6.2 | 0.06 | 0.55 | F(5,25)  = 0.6 | 0.69 | 0.11 |
| (α=0.013) | SEM | 17.4 | 12.4 | 9.0 | 10.6 | 12.9 | 12.8 | 14.6 | 14.5 | 14.1 | 12.8 | 16.1 | 12.5 |  |  |  |  |  |  |  |
| “I feel *Sleepy*” | M | 30.0 | 40.7 | 47.0 | 50.7\* | 57.5 | 56.0 | 36.3 | 39.2 | 34.0 | 29.3 | 23.5 | 28.0 | 6 | F(1,5) = 2.6 | 0.17 | 0.34 | F(5,25)  = 3.1 | 0.03 | 0.38 |
| (α=0.013) | SEM | 16.6 | 13.9 | 12.2 | 10.4 | 14.7 | 12.1 | 16.4 | 15.8 | 16.4 | 16.5 | 12.9 | 15.0 |  |  |  |  |  |  |  |
| **“*Strength”*** | **M** |  | **66.3** | **50.2** | **40.3** | **37.5** | **33.3** |  | **21.2** | **12.3** | **10.5** | **8.8** | **10.5** | **6** | **F(1,5)**  **=10.8** | **0.02** | **0.68** | F(4,20)  =2.39 | 0.09 | 0.32 |
| (α=0.025) | **SEM** |  | **14.1** | **10.7** | **8.9** | **10.0** | **11.2** |  | **11.5** | **9.8** | **7.2** | **7.5** | **9.6** |  |  |  |  |  |  |  |
| “Desire to *Take Again*” | M |  | 34.7 | 34.3 | 41.2 | 33.0 | 31.7 |  | 29.0 | 26.8 | 26.5 | 25.2 | 12.2 | 6 | F(1,5)  = 0.6 | 0.47 | 0.12 | F(1.8, 9.1)= 0.9 | 0.43 | 0.16 |
| (α=0.025) | SEM |  | 10.3 | 11.1 | 12.2 | 8.1 | 9.6 |  | 13.6 | 12.4 | 12.0 | 12.5 | 8.7 |  |  |  |  |  |  |  |
| **B) CONTROLS (n=6)** | |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **“I feel a *Good Drug effect*”** | **M** | **0.0** | **54.8** | **38.2** | **28.3** | **12.8** | **11.3** | **0.0** | **7.5** | **5.3** | **12.5** | **12.5** | **13.3** | 6 | F(1,5)  = 3.6 | 0.12 | 0.42 | **F(5,25) = 3.8** | **0.01** | **0.43** |
| (α=0.013) | SEM | 0.0 | 12.6 | 12.9 | 13.9 | 8.8 | 9.5 | 0.0 | 3.4 | 5.1 | 12.5 | 12.5 | 13.3 |  |  |  |  |  |  |  |
| “I feel a *Bad Drug effect*” | M | 0.0 | 0.2 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 14.8 | 0.0 | 0.0 | 0.0 | 0.0 | 6 | F(1,5)  = 1.0 | 0.37 | 0.16 | F(5,25)  = 1.0 | 0.45 | 0.16 |
| (α=0.013) | SEM | 0.0 | 0.2 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 14.8 | 0.0 | 00 | 0.0 | 0.0 |  |  |  |  |  |  |  |
| “I feel *Alert*” | M | 46.5 | 48.7 | 48.8 | 45.5 | 45.2 | 44.5 | 44.8 | 42.5 | 38.3 | 44.8 | 35.3 | 30.8 | 6 | F(1,5) = 1.8 | 0.24 | 0.27 | F(5,25)  = .45 | 0.81 | 0.08 |

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| (α=0.013) | SEM | 17.4 | 12.4 | 9.0 | 10.6 | 12.9 | 12.8 | 14.6 | 14.5 | 14.1 | 12.8 | 16.1 | 12.5 |  |  |  |  |  |  |  |
| “I feel *Sleepy*” | M | 10.0 | 14.3 | 14.8 | 16.2 | 13.2 | 11.5 | 15.8 | 17.0 | 31.2 | 24.2 | 17.8 | 14.0 | 6 | F(1,5)  = 7.1 | 0.04 | 0.59 | F(5,25)  = 1.6 | 0.19 | 0.24 |
| (α=0.013) | SEM | 8.5 | 8.6 | 7.4 | 9.8 | 9.2 | 10.9 | 9.0 | 9.7 | 13.2 | 12.3 | 10.9 | 11.9 |  |  |  |  |  |  |  |
| **“*Strength”*** | **M** |  | **52.0** | **50.0** | **37.8** | **49.5** | **49.5** |  | **6.8** | **1.3** | **2.7** | **2.7** | **13.5** | 6 | **F(1,5)**  **=19.0** | **0.007** | **0.79** | F(2.0,  10.1)  = 0.6 | 0.57 | 0.11 |
| (α=0.025) | SEM |  | 9.2 | 11.0 | 15.9 | 13.8 | 12.1 |  | 4.4 | 0.7 | 2.3 | 2.3 | 10.5 |  |  |  |  |  |  |  |
| “Desire to *Take Again*” | M |  | 53.5 | 53.8 | 54.2 | 48.3 | 53.7 |  | 21.8 | 25.5 | 33.0 | 33.0 | 32.0 | 6 | F(1,5)  =3.0 | 0.15 | 0.37 | F(4,20)  = 0.9 | 0.48 | 0.15 |
| (α=0.025) | SEM |  | 10.4 | 9.6 | 10.8 | 9.9 | 12.7 |  | 8.2 | 13.2 | 13.2 | 13.2 | 14.7 |  |  |  |  |  |  |  |
| B, baseline; VAS-P, Visua l Ana logue Scale – Psychosis Form; M, mean; SEM, standard error of measurement. **Bold** indicates a significant main effect of drug condition or drug condition× time interaction according to the corrected alpha. For every significant interaction, a difference between active and placebo cannabis at specific timepoints is indicated by\**p* < the corrected alpha. | | | | | | | | | | | | | | | | | | | | |

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1. Additional methodological details can be found in Vadhan et al. (2017) [↑](#footnote-ref-1)