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Intoxication by a synthetic cannabinoid (JWH-018) causes cognitive and psychomotor impairment in recreational cannabis users

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ABSTRACT

Background: Smoking mixtures containing synthetic cannabinoids (SCs) have become very popular over the last years but pose a serious risk for public health. Limited knowledge is, however, available regarding the acute effects of SCs on cognition and psychomotor performance. Earlier we demonstrated signs of impairment in healthy volunteers after administering one of the first SCs, JWH-018, even though subjective intoxication was low. In the current study, we aimed to investigate the acute effects of JWH-018 on several cognitive and psychomotor tasks in participants who are demonstrating representative levels of acute intoxication.

Methods: 24 healthy cannabis-experienced participants took part in this placebo-controlled, cross-over study. Participants inhaled the vapor of 75 μg JWH-018/kg body weight and were given a booster dose if needed to induce a minimum level of subjective high. They were subsequently monitored for 4 h, during which psychomotor and cognitive performance, vital signs, and subjective experience were measured, and serum concentrations were determined.

Results: Maximum subjective high (average 64%) was reached 30 min after administration of JWH-018, while the maximum blood concentration was shown after 5 min (8 ng/mL). JWH-018 impaired motor coordination (CTT), attention (DAT and SST), memory (SMT), it lowered speed-accuracy efficiency (MFFT) and slowed down response speed (DAT).

Conclusion: In accordance with our previous studies, we demonstrated acute psychomotor and cognitive effects of a relatively low dose of JWH-018.

1. Introduction

Over the last decade, synthetic cannabinoids (SCs) have become a popular replacement for natural cannabis in many countries (European Monitoring Centre for Drugs and Drug Addiction, 2019; European Monitoring Centre for Drugs and Drug Addiction, 2017). Typical brand names of smoking mixtures containing SCs include Spice, K2, and Yucatan Fire, but hundreds of brands have flooded the market since about 2008. Popularity was mainly sparked because of the unregulated status of these products at that time, the lack of detectability in standard drug tests, and the easy accessibility via the internet. Especially among deprived populations such as prison inmates or homeless people, SCs are particularly attractive because they are widely available, easily trafficked, and low priced (Gray et al., 2020; Ralphs et al., 2017; Clancy et al., 2018). However, SCs pose a serious concern for public health as they cause much more serious psychological effects and the risk for overdosing is considerably higher than natural cannabis (Tournebize et al., 2017; Tait et al., 2016; Hermanns-Clausen et al., 2013; Akram et al., 2019).

The first SCs were developed more than 40 years ago to study the endogenous cannabinoid system (Wiley et al., 2011). Around 2000, however, these chemical formulas were picked up by clandestine chemists who offered them as 'legal highs'. In 2008, JWH-018 was listed as the first non-classical cannabinoid in the European Monitoring Centre for Drugs and Drug Addiction report. This was almost immediately followed by nine more SCs, which resulted from pharmaceutical research

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labs (European Monitoring Centre for Drugs and Drug Addiction, 2009). Since then, the number of new synthetic cannabinoids coming onto to market increased rapidly, as it appeared relatively easy to develop SC analogues. The development of these new analogues was boosted as manufactures tried to stay ahead of legislation (Fattore and Fratta, 2011; United Nations Publications, 2019). By 2018, the EMCDDA already reported 190 SCs (European Monitoring Centre for Drugs and Drug Addiction, 2019). Although the numbers have stabilized somewhat during the last years, synthetic cannabinoids are still widely used and made up 50% of the novel psychoactive substances seized in the EU, Norway and Turkey in 2017 (European Monitoring Centre for Drugs and Drug Addiction, 2019). Also JWH-018 is still present on the drug market in many countries (Oberenko et al., 2019; Vučinić et al., 2018; Darke et al., 2020).

The strong psychoactive effects of SCs are attributed to the high binding affinities for the cannabinoid receptor type 1 (CB1), which in some cases is 100 times higher than THC (Uttl et al., 2018; Castaneto et al., 2014; Wiley et al., 2016), and that most act as a full agonist of CB1 (Potts et al., 2020; Gurney et al., 2014). This leads to potent cannabimimetic effects in animals, inducing hypomotility, catalepsy, hypothermia, and analgesia (Wiley et al., 2014). In humans, a lot of what we know about the effects of SCs comes from emergency units, poisoning centers, and case reports. These have demonstrated that the most common effects of SCs include tachycardia, agitation, and nausea but also psychosis and seizures (Gurney et al., 2014; Tait et al., 2016). SCs have also been implicated in some cases of mass poisoning and in a number of deaths (Adams et al., 2017; Tait et al., 2016; Darke et al., 2020). Cases from emergency and poisoning centers, however, only represent the most severe instances of intoxication and focus mainly on adverse physical effects but provide little insight into the psychoactive effects experienced.

A valuable insight into the psychoactive effects experienced by SC consumers comes from surveys, self-reports from internet forums, and non-acute cross-sectional comparisons (see (Akram et al., 2019) for an overview). In general, these show that the effects of SCs are similar, though stronger than those of cannabis (Fattore and Fratta, 2011; Akram et al., 2019). Due to the drugs' strong effects, many SC users still prefer cannabis over SCs (Castaneto et al., 2014). Typically, users report a quick onset of symptoms, which can last for a couple of hours. These symptoms include feelings of well-being, relaxation, perceptual alterations, but also anxiety, sedation and impairments in memory, attention and motor skills (Spaderna et al., 2013; Musshoff et al., 2014). A non-acute cross-sectional comparison with SC users, recreational users of cannabis and non-users, demonstrated SC users to be impaired in tasks of working memory, cognitive inhibition, and long term memory (Cohen et al., 2017). However, the authors could not rule out that this finding resulted from differences in educational levels. Unfortunately, these surveys and user reports provide no information on which specific SC was used and in which dose. Given the continuously changing content of smoking mixtures on the market, it is therefore difficult to draw conclusions about the cognitive effects of specific SCs.

Despite SCs dominating the drug market for more than ten years, controlled administration studies with SCs are scarce, mainly due to ethical and safety considerations. In 2009, a first self-experiment was conducted in two researchers who smoked a cigarette containing 'Spice Diamond' (Auwärter et al., 2009). They reported acute effects like altered mood and perception and feelings of impairment, although this last finding was not confirmed with an objective psychomotor test. In another study, two participants smoked 50 μg JWH-018/kg body weight (i.e. 3.6 and 4.2 mg JWH-018), and demonstrated acute effects like sedation and thought disruption (Teske et al., 2010). Both participants reported feelings of tiredness and exhaustion up until 12 h after smoking (Teske et al., 2010). The effects of two different doses of JWH-018 (inhaled) were investigated by our group in a small scale study (N = 6) with a randomized, within-subjects, placebo-controlled design (Theunissen et al., 2018). The doses of 2 and 3 mg were well-tolerated by cannabis-experienced participants, and there were no serious health issues reported within the 72 h after drug administration. Subjective high scores and serum drug concentrations were generally low and not fully representative of recreational use. Nonetheless, signs of neurocognitive impairment and subjective feelings of high did emerge, particularly after the 2 mg dose. Although it was expected that the applied doses would have comparable behavioral effects as an average dose of cannabis, the demonstrated effects turned out to be less potent than expected. Therefore, a higher dose and a larger sample size was used in an extension of the study (Theunissen et al., 2019). In this study with 17 participants, 75 μg JWH-018/kg body weight (inhaled) caused subjective intoxication in about half of the participants (responders), while the other half did not feel intoxicated after inhalation. These responders, showed significantly higher serum concentrations of the drug, demonstrated increased scores on psychotomimetic measures and impairment in reaction time tests. These latter two studies demonstrated that variations in drug delivery probably contributed to the discrepancy in drug response, as JWH-018's impairing effects on cognition and subjective measures were mainly demonstrated in participants who experienced a subjective intoxication of the drug.

We used a self-developed smoking device in our prior two studies. This consisted of a crack pipe that was heated over a flame, attached to a plastic tube and mouthpiece. During administration, it was inevitable that some vapor escaped. Also, when a participant did not inhale deeply enough, he or she probably did not receive the full dose. Subsequent heating of the pipe did not produce any more vapor; therefore, a second inhalation was ineffective. On top of that, analyses of the pipes showed that there was considerable residue left behind (Theunissen et al., 2018). Consequently, we searched for a better administration device, where we have better control over the temperature and avoid vapor from escaping.

Therefore, in the current study, we aimed to diminish this variability in the level of intoxication by using a better administration method and ascertain subjective intoxication when assessing the cognitive and psychomotor effects of JWH-018.

2. Materials and methods

The study was approved by the standing Medical Ethics Committee of the Academic Hospital and Maastricht University and it was carried out in compliance with the current revision of the Declaration of Helsinki (amended in 2013, Fortaleza) and the International Conference on Harmonization guidelines for Good Clinical Practice. A permit for obtaining, storing, and administering JWH-018 was obtained from the Dutch drug enforcement administration. All participants gave written informed consent and received financial compensation for their participation.

2.1. Participants

This study included a total of 24 occasional users of cannabis. Participants were recruited locally via advertisements and were subsequently screened using a health questionnaire and a medical examination (including an electrocardiogram, laboratory analyses, and drug and pregnancy screening). Only occasional cannabis use (minimally 1-year experience with cannabis, with a minimum and maximum use of 12 and 120 times/year) was permitted in order to exclude tolerance for the effects of cannabis (Ramaekers et al., 2020). Further inclusion criteria included: free from psychotropic medication; good physical health as determined by medical examination and laboratory analysis (hematology, blood chemistry, and urinalysis); absence of any significant medical, endocrine, and neurological condition; body mass index (weight/heigth^2) between 18 and 28 kg/m^2; written informed consent. Participants were excluded when they met one of the following criteria: prior experience with SCs, excessive drinking (> 20 alcoholic consumptions/week); excessive smoking (>25 cigarettes/day), pregnancy or lactation or failure to use contraceptives; hypertension

(diastolic>90 mmHg; systolic>140 mmHg), a history of psychiatric disorders, and a history of drug abuse.

2.2. Design and treatments

A placebo-controlled, double-blind, within-subjects design was used in this study. Each participant inhaled the vapor of JWH-018 (75 μg/kg body weight + booster dose when necessary) or placebo, on two separate test days. The order of the drug conditions was counterbalanced across participants and test days were separated by a minimum wash-out period of 7 days to avoid cross-condition contamination.

JWH-018 powder was purchased from THC Pharm GmbH (Germany). Placebo consisted of Knaster Hemp (Zentauri, Germany), a herbal blend with hemp aroma (0% THC). JWH-018 powder or Knaster was put in the filling chamber of a vaporizer pen (Puffco plus®, Los Angeles, USA), which was then heated up to approximately 380 °C. Neither of the drugs produced a typical (cannabis) odor. Participants inhaled the vapor in five intakes, according to a strict inhalation regimen (i.e. inhale deeply for 5 s, hold the breath for 5 s, exhaling). A booster dose of 50 μg/kg body weight was administered in case participants did not show a subjective response (i.e., a minimum subjective high score 30% was required) within 15 min after administration of JWH-018. Preparation of the vaporizer and the administration was done by a researcher who was not involved in the study assessments.

For the first administration, participants received an average dose of 4.97 mg (min = 3.75; max = 6.67 mg) JWH-018. Four participants did not show a subjective response (i.e., <30% of the maximum possible response) within 15 min after administration and were therefore given a booster dose (average = 3.26 mg). These four participants reached sufficient intoxication 15 min after the booster dose (i.e., average 58% compared to 63% in the group who received only one administration). The total average dose was 5.52 mg.

2.3. Subjective high

Subjective high is self-rated on a 10 cm Visual Analogue Scale (VAS), with 0 indicating 'not high at all', and 10 (or 100%) indicating 'extremely high'. Subjective high was rated at regular intervals during the test day (see Table 1).

2.4. Cognitive and psychomotor performance tests

A battery of cognitive tests was included, which was previously demonstrated to be sensitive to the effects of a moderate to high dose of cannabis (Ramaekers et al., 2006c; Ramaekers et al., 2009; Ranganathan and D'Souza, 2006; Desrosiers et al., 2015).

2.4.1. Critical Tracking Test (CTT)

The CTT is a psychomotor test which assesses the participant's ability to control a displayed error signal in a first-order compensatory tracking task (Jex et al., 1966). Error is displayed as a horizontal deviation of a cursor from the midpoint on a horizontal, linear scale. Compensatory joystick movements null the error by returning the cursor to the midpoint. Total duration of the task is approximately 3 min. The frequency at which the participant loses control is the critical frequency or lambda-c (λ_c). The test included five trials, of which the lowest and the highest score were removed; the average of the remaining scores is taken as the final CTT-score.

2.4.2. Divided Attention Task (DAT)

The DAT measures the ability to divide attention between two tasks performed simultaneously (Moskowitz, 1973). Participants have to perform the same tracking task as described above, but now at a constant level of difficulty. As a secondary task, the subject monitors 24 single digits which are presented in the corners of the computer screen. The participants are instructed to react to the target number '2' by removing their foot as fast as possible from a pedal switch. Duration of the task is 12 min. The mean absolute tracking error (in mm) and the number of control losses are the performance measures of the primary task. The number of misses, false alarms and mean reaction time (msec) of the responses to the target number, are the performance measures in the secondary task. Performance in this test has proven to be sensitive to the effects of many sedative drugs (Robbe and O'Hanlon, 1995; Ramaekers et al., 2009; Jongen et al., 2014; Vermeeren et al., 2002).

2.4.3. Spatial Memory Task (SMT)

In this task (adapted from (Kessels et al., 1999)), ten black-and-white pictures are presented subsequently in 10 different locations on a computer screen. After the presentation, each picture is presented alone with two possible locations where it appeared. Participant's task is to choose the correct location, a measure of the immediate recall. This procedure is repeated six times, with different stimuli and locations. After a 30-min delay, the recall phase is repeated; this test serves as a delayed recall measure. The immediate recall phase takes about 8 min; the delayed recall part about 5 min.

2.4.4. Stop Signal Task (SST)

The SST measures motor impulsivity, which is defined as the inability to inhibit an activated or pre-cued response leading to errors of commission. The current test is adapted from an earlier version (Fillmore et al., 2002) and has been validated for showing stimulant and sedative drug effects (Ramaekers and Kuypers, 2006). The task requires participants to make quick responses to visual go-signals and to inhibit their response if a subsequent visual stop-signal, i.e., "*", appears in one of the four corners of the screen. Total task duration is approximately 8 min. Dependent variables are go reaction time (ms), stop reaction time, number of correct responses, omission (not responding on go-trials), and commission errors (not inhibiting a response to a no go trial). Stop reaction time represents the estimated mean time required to inhibit a response. Stop reaction time is calculated by subtracting the stop signal

Table 1
Overview of the activities during the test day relative to drug administration (* relative to time of administration or the last booster dose in cases where this was needed).

Time *	Subjective high	Blood sample	CTT	DAT	SMT	SST	MFFT	DSST	TOL
baseline	x	x	x					x	
5 min	x	x							
15 min	x	x	x				x		
30 min	x	x			x				
45 min	x	x							
1 h	x	x		x	x	x			
1 h30		x							
2 h	x	x							
2 h30			x	x					x
3 h	x	x							
4 h	x	x						x	

delay from the reaction time on go-trials associated with n^{th} percentile of the reaction time (RT) distribution (Logan, 1994).

2.4.5. Matching Familiar Figures Test (MFFT)

The MFFT measures reflection impulsivity, which is the tendency to reflect on the validity of problem-solving under the particular condition of several possible alternatives. The test involves simultaneous presentation of a target figure positioned on the left of the screen and an array of six alternatives on the right half of the screen, all except one differing in one or more details from the target figure. The participants are asked to select from the alternatives, the figure that exactly matches the target figure, as quickly as possible. Task duration is approximately 5 min. Two dependent measures, mean latency to first response (ms?) and the total number of errors, are automatically recorded. In addition, an impulsivity score (I-score) is calculated by subtracting the standard score of the mean latency to the first response from the standard score of the total number of errors committed. An efficiency score (*E*-score) is calculated by summing the standard score of the mean latency to the first response with the standard score of the total number of errors committed.

2.4.6. Digit Symbol Substitution Task (DSST)

The DSST is a computerized version of the original paper and pencil test taken from the Wechsler Adult Intelligence Scale (Mcleod et al., 1982). The participant is required to match each digit with a symbol from the encoding list as rapidly as possible. The number of correctly encoded digits within 3 min, are the performance measures.

2.4.7. Tower of London (TOL)

The Tower of London (TOL) is a decision-making task that measures executive function and planning (Shallice, 1982; Sobczak et al., 2002). The task consists of 44 computer-generated images of begin- and end-arrangements of three colored balls on three sticks. The participant's task is to determine as quickly as possible whether the end-arrangement can be accomplished by "moving" the balls in two to five steps from the beginning arrangement by pushing the corresponding number-coded button. Duration of the task is dependent of the response speed of the participant, but is approximately 8–12 min. The total number of correct decisions and the average RT for correct decisions are the main performance measures.

2.5. Pharmacokinetics

Ten blood samples (5 mL) were taken during each test day (see Table 1). These were centrifuged, and serum was frozen at −20 °C until pharmacokinetic assessments. The samples were fortified with the internal standard d_9-JWH-018. Afterwards the samples were salted out by adding ammonium formate (10 M) and were precipitated with acetonitrile. After centrifugation, the supernatant was evaporated and reconstituted in mobile phase. The analysis was performed with an Ultimate 3000RS UHPLC (Dionex, USA) coupled to a QTRAP® 6500 triple quadrupole-linear ion trap instrument (SCIEX, Darmstadt) in MRM mode. Two MRM transitions were recorded and concentrations of JWH-018 were determined using an external calibration.

2.6. Safety

Heart rate and blood pressure (systolic and diastolic) were measured at baseline and regular intervals after administration (every 10 min within the first hour, every 15 min within the second hour, and subsequently each half-hour until the end of the test day).

2.7. Procedures

Participants were instructed to continue their cannabis use as usual but were requested to abstain from cannabis from about five days before and during the test days. They were also required to refrain from using alcohol or caffeine on the test day and the day before testing. Cigarette smoking was prohibited for 30 min before and during test days. Participants were asked to arrive at the testing facilities well-rested. On each test day, participants were instructed to have a standard breakfast (excluding caffeine products) before coming to the site, while lunch was provided at the site.

Testing took place at the testing facilities at Maastricht University. On arrival, participants were screened for drugs or their metabolites (THC, opiates, cocaine, amphetamine) in urine, and for alcohol in breath. For women, a urine pregnancy test was also performed. When all tests turned back negative, an intravenous catheter was placed in the lower arm. Urine and blood samples were taken at baseline and at the end of each test day to perform laboratory safety analyses (hematology and blood chemistry, urinalysis). Two short cognitive tasks were performed at baseline (CTT and DSST) to check for baseline difference between test days. Subsequently, the drug/placebo administration was performed. Cognitive and psychomotor performance was measured at regular intervals within a 4.5-h after administration (see Table 1). Timing of the tasks was chosen to measure most of the cognitive functions at least once within the first hour after administration. Different versions (i.e., different stimuli or different order) of the SMT, MFFT, DSST and TOL were used for the two test days to avoid learning effects. The test battery included additional questionnaires measuring psychotomimetic effects (Theunissen et al., 2021). Blood samples were taken at regular intervals during the test days to determine pharmacokinetics. At the end of the test day, participants were asked about adverse events they experienced and were given a diary on which they had to note possible side effects they experienced until 72 h after administering the drug. Participants were required to stay at the test facility until they had a score lower than 10% on VAS scales measuring intoxication and sedation, and the experimenters judged that they were no longer intoxicated or sedated.

2.8. Statistical analyses

GLM Repeated Measures ANOVA, with Drug (placebo and JWH-018) and Time as within-subject factors, was used for tests that were repeated during the test day (CTT, DAT, SMT, DSST, and VAS). GLM Univariate ANOVA with Drug (placebo and JWH-018) as a within-subject factor was used for all other tests. A Greenhouse-Geisser correction was applied in case of sphericity violation. In case of significant Drug x Time interactions, separate drug-placebo contrasts were conducted, and sequential Bonferroni correction was applied to correct for multiple comparisons (Overall and Rhoades, 1987). Non-normal distributed data (i.e. skewness >0.5 or < -0.5) was analyzed with a Wilcoxon signed-rank test. One sided-testing was used for cognitive and psychomotor measures, as it is expected that JWH-018 causes impairment. A p-value of <0.05 was considered statistically significant. Partial eta squared (partial η^2) is reported to demonstrate the effect's magnitude and is based on Cohen's f, which defines small, medium and large effect sizes as respectively 0.10, 0.25, and 0.40, which corresponds to partial η^2 values of 0.01, 0.06, and 0.14 (Richardson, 2011). All statistical tests were conducted using IBM SPSS statistics, version 26.

2.9. Missing data

Subjective high scores were not completed at all time points by all participants. This was the case for two participants in the placebo condition (missing 3 and 4 consecutive data points) and six participants in the JWH-018 condition (missing 4, 3, 2 ($N = 2$) consecutive data points, and 1 ($N = 2$) data point). Therefore, the missing data of these participants were replaced by the sample average subjective high scores of the Drug condition on that particular time point, before entering the RM ANOVA analysis. There was missing data of the CTT (1 time point) for two participants in the JWH-018 condition and one in the placebo condition. Three participants in the JWH-018 condition and two in the

placebo condition missed one measurement of the DAT. Unit imputation was done by taking the average value of the two scores on the other time points (when the middle score was missing in the CTT), taking the value of the next time point (when the first score was missing) or taking the value of the previous time point (when the last score was missing) of that participant. In the JWH-018 condition, scores for one participant were missing for the SST and SMT, while one participant was unable to perform the MFFT in the placebo condition. As these tests were only taken once (except the SMT, but immediate and delayed memory scores are not comparable), mean imputation was done by taking the average score of that variable in that Drug condition.

It was not possible to draw blood from one participant, while for three participants, only two samples could be taken (baseline and 5 or 15 min after administration). For three other participants, 2, 3, or 4 samples were missing (samples taken included at least the baseline, the 5 and 15-min sample). Blood pressure and heart rate data were not complete for four participants in the JWH-018 condition (missing 1, 4, 6, and 13 time points). Missing data from blood samples or vital signs were not replaced, as these were not the primary outcome measures of this study.

3. Results

Data from all participants (10 males, 14 females) was analyzed. Mean age (SD, min-max) of the participants was 22.8 years (3.05, 18.9–33.6), and on average, they had been using cannabis for 4.5 years (2.15, 1–9), 3.4 times a month (2.3, 1–10).

3.1. Safety

Laboratory safety analyses showed no clinically relevant deviations from the normal ranges. Three participants reported nausea and/or stomach ache after JWH-018 administration; one of these participants had to lay down for about an hour. Three participants reported dry mouth. Two participants reported a short moment of increased energy followed by a feeling of tiredness, while a third participant only reported sedative feelings. Two participants reported headaches, and one participant reported paranoid feelings. In the placebo condition, five participants reported headaches, while one participant reported dizziness.

Mean systolic and diastolic blood pressure and heart rate are shown in Fig. 1 (Panel A-C). The analysis reported a significant Drug ($F_{1,18} = 9.28$; $p < .01$; $\eta_p^2 = 0.34$), Time ($F_{6.25,112.4} = 13.16$; $p < .001$; $\eta_p^2 = 0.42$) and Drug x Time ($F_{5.45,597} = 4.72$; $p < .001$; $\eta_p^2 = 0.21$) effect on heart rate. Bonferroni-corrected drug-placebo contrasts showed that at 10 min ($F_{1,20} = 15.23$; $p < .01$; $\eta_p^2 = 0.43$), 20 min ($F_{1,20} = 16.98$; $p < .01$; $\eta_p^2 = 0.46$), 50 min ($F_{1,20} = 12.0$; $p < .0038$; $\eta_p^2 = 0.39$), and 3 h ($F_{1,20} = 12,78$; $p < .0036$; $\eta_p^2 = 0.38$) after administration of JWH-018, heart rate was significantly increased compared to placebo. A significant main effect of Time was also demonstrated on systolic blood pressure ($F_{15,285} = 4.09$; $p < .001$; $\eta_p^2 = 0.18$), showing a decrease within the first hour, followed by a slow and unsteady increase. There was no main Drug, Time, or Drug x Time interaction effect on diastolic blood pressure.

3.2. Subjective high

Mean subjective high scores are shown in Fig. 2 (Panel A and C). Average subjective intoxication five minutes after administration (or booster) was 49%, while maximal subjective intoxication was reached 30 min post-administration (64%).

GLM Repeated measures ANOVA showed a significant main effect of Drug ($F_{1,23} = 176.4$; $p < .001$; $\eta_p^2 = 0.89$) and Time ($F_{3.4,77.2} = 62.6$; $p < .001$; $\eta_p^2 = 0.73$), and a Drug x Time interaction ($F_{3.8,87.1} = 133.6$; $p < .001$; $\eta_p^2 = 0.67$) on the subjective high scores. Bonferroni-corrected drug-placebo contrasts demonstrated that at all time points after administration, subjective high scores were significantly higher after JWH-018 compared to placebo ($F_{1,23}$ between 25.76 and 209.39; $p < .01$; η_p^2 between 0.53 and 0.90).

3.3. Pharmacokinetics

Maximal JWH-018 concentrations in serum ranged from 1.07 to 22.45 ng/mL (mean = 8.00; SD = 2.81). Mean JWH-018 concentrations over time are given in Fig. 2 (panel B and C). For 20 participants, the highest drug concentration was observed at 5 min after inhalation. For one participant, the peak concentration was at 15 min post-administration, while two other participants either missed the 5-min sample or the 15-min sample.

3.4. Cognitive and psychomotor tests

In the Critical Tracking task, baseline scores did not show significant drug-placebo differences; therefore, a baseline correction was not applied. CTT-scores showed a significant main effect of Drug ($F_{1,23} = 8.26$; $p < .01$; $\eta_p^2 = 0.26$) and Time ($F_{1.41,32.39} = 2.67$; $p = .05$; $\eta_p^2 = 0.10$), being lower for JWH-018 immediately after administration (see Fig. 3A). The Drug by Time interaction was not statistically significant.

Main effects of Drug were also demonstrated in the Divided Attention Task, with JWH-018 significantly impairing tracking error (Fig. 3B) ($F_{1,23} = 10.631$; $p < .01$, $\eta_p^2 = 0.32$) and slowing down reaction time ($F_{1,23} = 7.31$; $p < .01$, $\eta_p^2 = 0.24$) (Fig. 3C). A significant main effect of Time was also demonstrated for tracking error which improved over time ($F_{1,23} = 5.54$; $p = .014$, $\eta_p^2 = 0.19$). A Wilcoxon Signed-rank tests showed that the number of control losses was significantly higher after JWH-018 administration at both time points ($Z = 3.65$ $p < .01$ and $Z = -2.52$ $p < .01$) (Fig. 3D). The number of misses and false alarms was significantly increased after JWH-018 at the first measurement ($Z = 2.38$

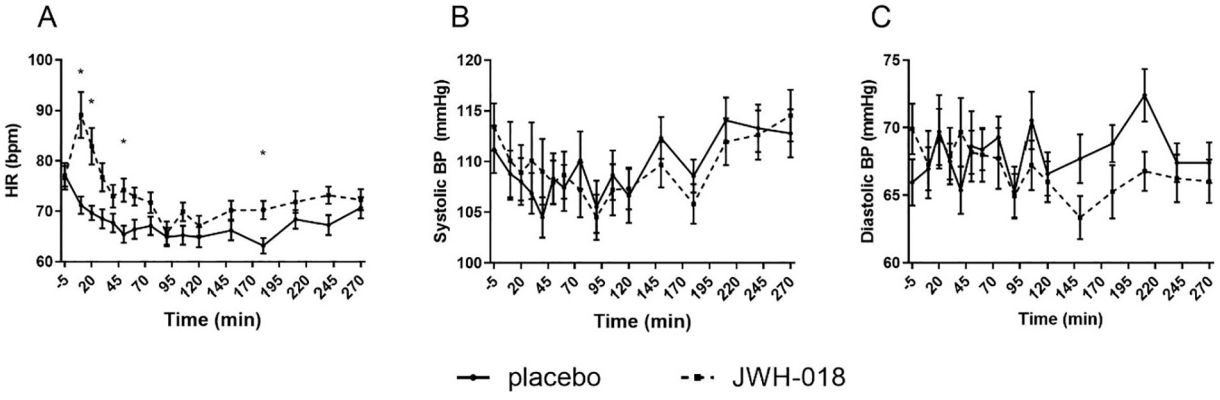

Fig. 1. Average (SEM) heart rate (HR) (panel A), systolic blood pressure (BP) (panel B), and diastolic blood pressure (panel C) over time for both JWH-018 and placebo. * significant drug-placebo contrast (sequential Bonferroni corrected).

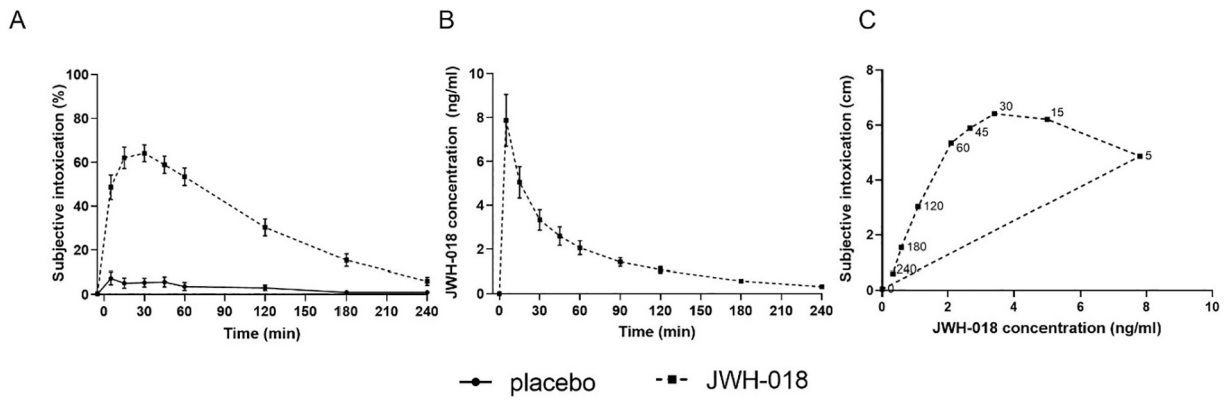

Fig. 2. Mean (SEM) subjective high score (A) and JWH-018 serum concentrations (B) over time after placebo and JWH-018 administration, and average subjective high score plotted against average JWH-018 serum concentrations over time after administration (C). * significant drug-placebo contrast (sequential Bonferroni corrected).

$p < .01$ and $Z = 2.61$ $p < .01$) but not at the second time point (Fig. 4E and F).

The number of correctly remembered locations in the Spatial Memory Task demonstrated a main effect of Drug with significantly lower scores due to JWH-018 ($F_{1,23} = 24{,}50$; $p < .01$, $\eta_p^2 = 0.52$), and a main effect of Time, with performance worsening over time ($F_{1,23} = 8.23$; $p < .01$, $\eta_p^2 = 0.26$) (see Fig. 4A). There was no Drug by Time interaction. Response time in the SMT was not significantly affected by Drug, Time, or Drug by Time.

The number of omission errors in the Stop Signal Task was significantly affected by Drug, with a significant increase due to JWH-018 administration ($Z = 1.93$ $p < .05$) (see Fig. 4B).

In the Matching Familiar Figures Test, the efficiency score but not the impulsivity score showed a significant effect of Drug ($F_{1,46} = 3.75$; $p < .05$, $\eta_p^2 = 0.07$), with a lower score after JWH-018 administration (see Fig. 4C).

Baseline scores in the Digit Symbol Substitution Task did not show significant drug-placebo differences; hence, baseline correction was not needed. Correct responses in the DSST showed a significant main effect of Time ($F_{1,23} = 8.68$; $p < .01$, $\eta_p^2 = 0.27$), i.e., the scores were lower at the end of the test day compared to baseline. No main Drug effect or Drug by Time interaction was shown on the number of correct responses in the DSST. No significant effect of Drug was found on any variable of the Tower of London.

4. Discussion

Despite the fact that SCs are a serious threat to public health and safety, our understanding of the acute effects of SCs on cognition and psychomotor performance is limited and mainly based on self-reports or on users who overdose on it. Two experimental studies in humans with JWH-018 have been conducted by our group earlier (Theunissen et al., 2018; Theunissen et al., 2019). These showed that relatively low doses (2–6.2 mg) caused some cognitive and psychomotor deterioration, but a critical drawback was that the drug did not cause intoxication in about half of the participants. With the present study, we aimed to fill the current knowledge gap by setting up a controlled study to evaluate the cognitive and psychomotor effects of acute intoxication with a SC, in a sufficiently large sample of healthy participants.

Twenty-four participants received a dose of 75 μg JWH-018/kg body weight and placebo on separate test days. Whereas in our previous studies, a self-developed inhalation device led to a suboptimal drug administration, this time a commercially available vaporizer pen was used to administer the drug. In four cases, the required minimum subjective intoxication was not reached within 15 min, therefore, these participants received a booster dose (average total dose of 5.52 mg of JWH-018). Maximum subjective intoxication (64%) was reached 30 min post-administration, which is comparable to the intoxication level observed in earlier studies with single-dose administrations of cannabis (THC 14.5–33 mg) (Theunissen et al., 2012; Hartman et al., 2016). The maximal serum concentration of JWH-018 in the current study (8.0 ng/mL) was comparable to what we have demonstrated earlier (7.49 ng/mL) (Theunissen et al., 2019). Nonetheless, the variation (SD) was considerably lower this time (2.81 vs. 5.66), indicating that the improved method of administration also led to more consistent levels in the blood. The current level of drug concentration is however significantly lower than what has been demonstrated in fatal cases which was up to 199 ng/mL (Shanks et al., 2012).

Compared to people ending up in poison centers or emergency departments, the participants in the current study were somewhat moderately intoxicated. Nonetheless, the current dose of JWH-018 significantly impaired most of the cognitive and psychomotor performance measures evaluated during the 4-h window after administration. The drug impaired motor coordination (CTT), attention (DAT and SST), memory (SMT), it lowered speed-accuracy efficiency (MFFT) and slowed down response speed (DAT). These functions have also been found to be impaired after the use of cannabis (with THC doses up to 500 μg/kg bodyweight) (Ramaekers et al., 2006b; Curran et al., 2002; Ranganathan and D'Souza, 2006). The magnitude of impairment caused by JWH-018 in the tracking task was higher than the impairment we have previously seen for 250 μg/kg bodyweight cannabis but lower than the 500 μg/kg dose (Ramaekers et al., 2006b). The number of omission errors in the SST showed a similar pattern, even though the task was performed 30 min earlier in the cannabis study (Ramaekers et al., 2006b). Efficiency score in the MFFT was taken at a similar time after administering cannabis (300 μg/kg dose) in another of our studies (van Wel et al., 2013). However, efficiency seemed to be somewhat more impaired as a result of cannabis than JWH-018. This is also the case for tracking error in the DAT, which seemed to be more sensitive for the effect of cannabis (van Wel et al., 2013) than for JWH-018. For memory performance, a direct comparison with cannabis is not possible as previous studies have used different memory tasks. It should be noted, however, that statistical comparisons are needed in order to make reliable conclusions about a direct comparison of the effect caused by JWH-018 and cannabis or other drugs.

In the current study, no effects were found on the TOL or the DSST, possibly because these were performed more than 2.5 h after administration and/or tasks are less sensitive for the impairing effects. JWH-018 caused a significant increase in heart rate, an effect that is also typical to cannabis use (Kelly et al., 1993; Ramaekers et al., 2009). Nonetheless, JWH-018 was overall well tolerated by the participants in this study.

As the current and previous studies have demonstrated, acute SC use produces rapid peak concentrations in blood, followed by a rapid decline (Theunissen et al., 2019; Castaneto et al., 2015; Teske et al., 2010). From

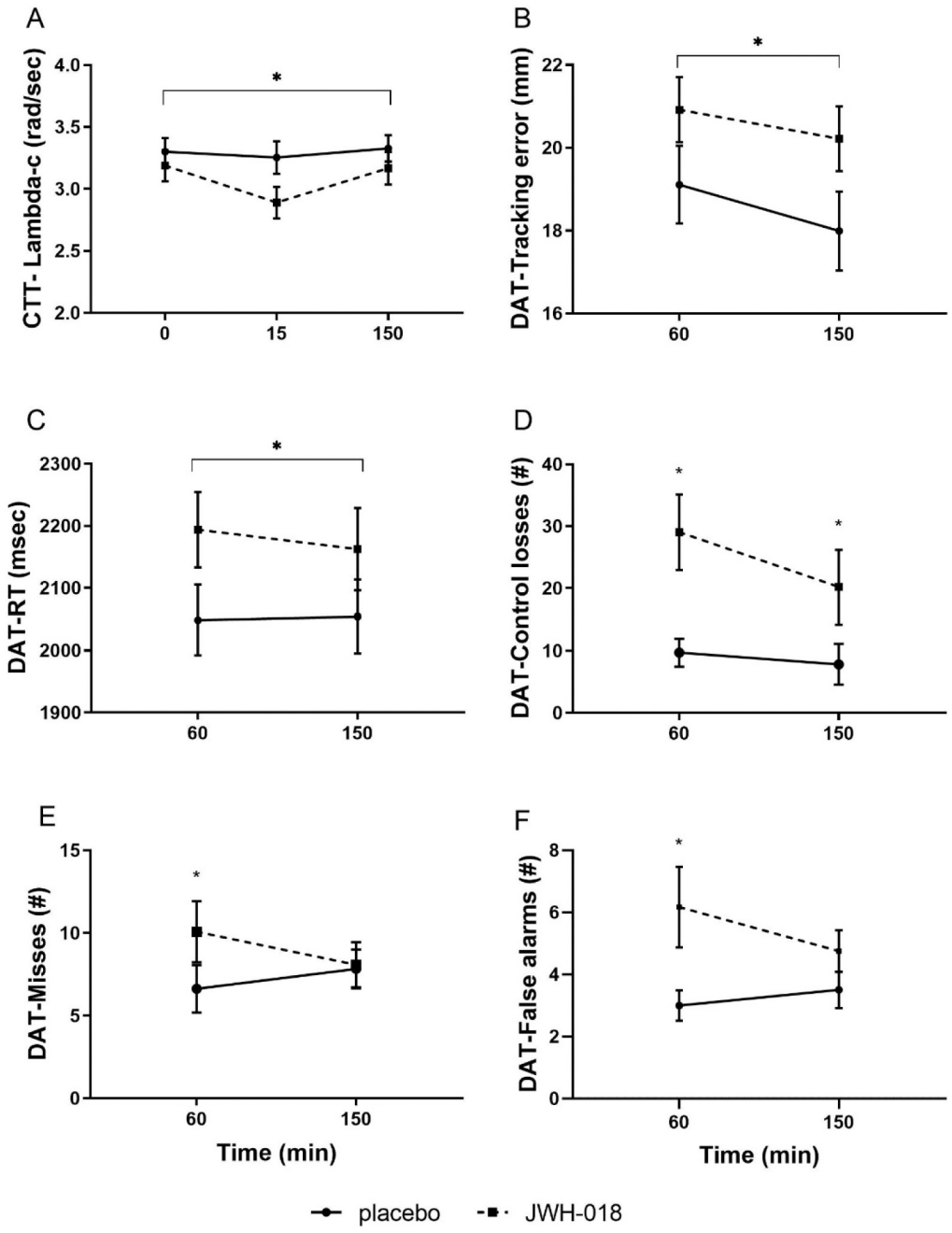

Fig. 3. Mean (SEM) values for lambda-c in the Critical Tracking task (A), tracking error (B), reaction time (C), number of control losses (D), misses (E) and false alarms (F) in the Divided Attention task. * Significant overall Drug effect. * Significant drug effect (Wilcoxon signed-ranked test).

this, it follows that blood concentrations of people who end up in emergency departments with intoxication symptoms, or those who are intercepted in traffic for suspected intoxication, are presumably already declined and not representative of the maximum concentration they experienced shortly after administration. In addition, the current study also replicates the counter-clockwise hysteresis loop between drug concentration and subjective intoxication, indicating that the peak in subjective intoxication is reached later than the peak concentrations of JWH-018 (Theunissen et al., 2019). This phenomenon is also typically seen after cannabis use indicating a distribution delay between the systemic drug concentration and the time to reach the site of action (Louizos et al., 2014). Therefore, it is expected that effects on cognition and psychomotor performance in users who use high amounts or overdose on SCs are even more problematic than what we have demonstrated in the current study. As shown previously, the inhomogeneity in smoking mixtures seriously challenges safe dosing of SCs (Moosmann et al., 2015), making it impossible for the user to predict the effects they will be experiencing.

As a result of intoxication with a SC, even without a full-blown subjective response, users can endanger themselves and others, i.e., in traffic situations. The impaired psychomotor functions and related risk for traffic safety are well known and studied in the context of cannabis and have led to specific laws regarding driving under the influence of cannabis and to road-side testing methods (Grotenhermen et al., 2007; Ramaekers et al., 2006a; Papafotiou et al., 2005). A few reports have been published in which SCs were detected in cases of suspected impaired driving (Chase et al., 2016; Yeakel and Logan, 2013; Musshoff et al., 2014). In these cases, concentrations of JWH-018 in blood mostly

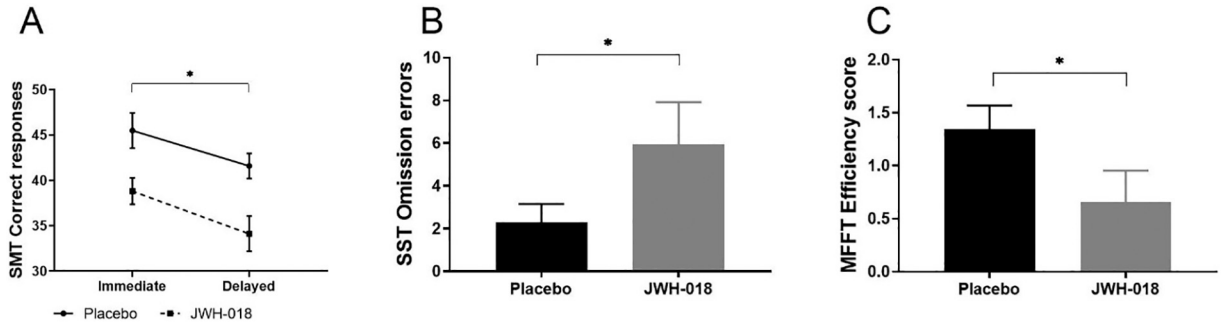

Fig. 4. Mean (SEM) values for the number of correct responses in the Spatial Memory task (A), the number of omission errors in the Stop Signal task (B), and efficiency score in the Matching Familiar Figures task (C). * Significant overall Drug effect.

ranged between 0.1 and 1.9 ng/mL, with two people having higher levels of 9.9 and 18 ng/mL. The observed performance impairment of the drivers was reported to be similar to what is typically seen with cannabis use (Musshoff et al., 2014), although drivers under the influence of SCs exhibited more signs of confusion or disorientation (Chase et al., 2016). In addition, Yeakel and Logan (2013) demonstrated signs of psychomotor impairment on the standard field sobriety test. SCs are however, not detectable in a standard drug test, making them an even greater hazard for traffic safety.

In the current study, a minimum dose of 75 μg JWH-018/kg body weight induced acute intoxication levels comparable to what is previously demonstrated with cannabis. Even though the participants well-tolerated the dose, JWH-018 acutely impaired performance in cognitive and psychomotor tasks in a 4-h window after administration, confirming our previous findings. Motor coordination (CTT), attention (DAT and SST), memory (SMT), speed-accuracy efficiency (MFFT), and response speed (DAT) were impaired, and this was most strongly demonstrated within the first 2.5 h after administration. However, this might still be an underestimation of the impairing effects of SC, as more potent SCs are widely available on the market and accidental overdosing is quite common. Therefore, more controlled studies with a broader range of different SCs are warranted.

CRediT authorship contribution statement

J.G.R, K.K and E.T. designed the study; J.T.R., N.H, and ET took care of study logistics and data acquisition; J.T.R. and E.T. processed the experimental data; S.W.T., M.A.N., and S.H. performed pharmacokinetic analyses, E.T. performed the analyses and drafted the manuscript. All authors discussed the results and commented on the manuscript.

Declaration of competing interest

All authors report to have no financial interests or potential conflicts of interest.

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