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Delta-9-tetrahydrocannabinol intoxication is associated with increased prefrontal activation as assessed with functional near-infrared spectroscopy: A report of a potential biomarker of intoxication

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ABSTRACT

The primary psychoactive compound in cannabis, Δ9-tetrahydrocannabinol (THC), binds to cannabinoid receptors (CB1) present in high concentrations in the prefrontal cortex (PFC). It is unknown whether the PFC hemodynamic response changes with THC intoxication. We conducted the first double-blind, placebo-controlled, cross-over study of the effect of THC intoxication on functional near infrared spectroscopy (fNIRS) measures of PFC activation. Fifty-four adult, regular (at least weekly) cannabis users received a single oral dose of synthetic THC (dronabinol; 5–50 mg, dose individually tailored to produce intoxication) and identical placebo on two visits at least one week apart. fNIRS recordings were obtained during a working memory task (N-Back) at three timepoints: before THC/placebo, at 100 min (when peak effects were expected), and at 200 min after THC/placebo administration. Functional data were collected using a continuous-wave NIRS device, with 8 sources and 7 detectors arrayed over the forehead, resulting in 20 channels covering PFC regions. Participants also completed frequent heart rate measures and subjective ratings of intoxication. Approximately half of participants reported significant intoxication. Intoxication ratings were not correlated with dose of THC. Increases in heart rate significantly correlated with intoxication ratings after THC dosing. Results indicated that 100 min after THC administration, oxygenated hemoglobin (HbO) response significantly increased from pre-dose HbO levels throughout the PFC in participants who reported significant intoxication. Changes in HbO response significantly correlated with self-reported intoxication at 100 min after THC administration. Among those who reported intoxication, HbO response decreased at 200 min after THC, when intoxication had largely resolved, compared to the peak THC time point. This study demonstrates that THC intoxication causes increased PFC activity, and fNIRS of the PFC can measure this effect. Increased neural activation in PFC represents a potential biomarker for cannabis intoxication.

1. Introduction

Cannabis is among the most widely used psychoactive substances in the United States and worldwide (SAMSHA, 2011). There is strong evidence that acute doses of Δ9-tetrahydrocannabinol (THC), the primary psychoactive compound in cannabis, affect cognitive function. In double-blind, placebo-controlled studies, oral administration of 40–300 μg/kg THC caused dose-dependent impairment on memory, divided and sustained attention, reaction time, visual tracking and motor function tasks (Ameri, 1999; Curran et al., 2002; D'Souza et al., 2004; Hall and Solowij, 1998; Hampson and Deadwyler, 1999; Leweke et al., 1998; Lichtman et al., 2002; Ramaekers et al., 2004). Many of these processes rely on activity in the prefrontal cortex (PFC), which coordinates neural activity related to executive control, decision-making,

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goal-directed behavior, selective attention, and working memory (Bechara et al., 1998; Euston et al., 2012; Hebscher et al., 2016; Hebscher and Gilboa, 2016). The PFC contains high concentrations of cannabinoid (CB1) receptors (Gardner, 2005), suggesting that characterization of the effects of THC on measures of neural activation in the PFC may provide important insight into the mechanism by which THC affects cognitive performance in those who are intoxicated from THC.

Cannabis is notable for its complex pharmacokinetics and pharmacodynamics that contribute to wide inter-individual variability in intoxication and cognitive impairment with a given dose, even among people with similar cannabis use patterns (Hollister, 1978; Gorelick et al., 2013; Ramaekers et al., 2016). High inter-individual variability in plasma and oral fluid pharmacokinetic parameters have been reported following smoking a single cannabis cigarette (Marsot et al., 2016) and oral ingestion of cannabis products (Newmeyer et al., 2017). A single dose of cannabis also causes variable impairment (Ramaekers et al., 2016) in cognitive domains including memory, divided and sustained attention, reaction time, visual tracking and motor function (Ameri, 1999; Curran et al., 2002; D'Souza et al., 2004; Hall and Solowij, 1998; Hampson and Deadwyler, 1999; Leweke et al., 1998; Lichtman et al., 2002; Ramaekers et al., 2004). Many of these cognitive processes rely on activity in PFC. This wide variability in subjective and cognitive response is likely due to tolerance among some cannabis users, defined as the need, following repeated exposure, for increasing amounts of cannabis to achieve intoxication, or a markedly diminished effect with continued use of the same amount of cannabis (APA, 1994). Here we propose that inter-individual variability in cognitive effects of THC may be detectable with measures of THC on PFC activation. In the current study, we aimed to characterize the effect of THC on PFC neuronal activation among those who became intoxicated.

We have previously reported increased PFC activity during a working memory task, assessed with functional near infrared spectroscopy (fNIRS) in a small cohort of young adult regular (weekly or more) cannabis users following a single, open-label dose of oral THC (Keles et al., 2017). In this study, the oxygenated hemoglobin (HbO) response following oral THC administration was greater in those who reported greater subjective intoxication effects of THC, termed high responders (HR). In contrast, those with lower subjective response (LR) to the dose of THC administered did not show a significant change in PFC activation following oral THC (Keles et al., 2017). This increased PFC activity is consistent with positron emission tomography (PET) studies that have demonstrated global increases in cortical activation following smoked cannabis or infused THC (Mathew et al. 1992, 1997). In these studies, hemispheric cerebral blood flow (CBF) increases correlated with intoxication ratings (Mathew et al., 1997). These findings, taken together raised the hypothesis that PFC activation, measured with fNIRS, could serve as a biomarker for cannabis intoxication.

Here we report an extension of our open-label findings from a double-blind, placebo-controlled, crossover design study evaluating the effects of THC intoxication on cortical hemodynamics in the PFC during the N-back working memory task in a larger sample with a cross sectional design. The N-back task reliably activates PFC structures in fNIRS studies, (Dommer et al., 2012; Kuruvilla et al., 2013; Aghajani and Omurtag, 2016; Aghajani et al., 2017; Vermeij et al., 2017; Tseng et al., 2018), as well as in functional MRI and EEG studies (see Wang et al., 2019 for a meta-analysis of 96 fMRI studies).

Based on these PET studies of cannabis intoxication (e.g. Mathew and Wilson, 1993; Mathew et al., 1999; Mathew et al., 1997; Volkow et al., 1996), and our prior fNIRS findings (Keles et al., 2017), we hypothesized that fNIRS measurements within the PFC would allow us to detect increased hemodynamic response during a working memory task after THC administration in regular cannabis users as a function of acute intoxication.

2. Methods

Study procedures were approved by the Partners Human Subjects Committee. All participants completed an informed consent process and provided written informed consent prior to initiation of study procedures. Participants were compensated for completion of each study visit.

2.1. Participants

Adults, aged 18–55, who reported at least weekly cannabis use were recruited through advertising in the community. Exclusion criteria included a negative screen for cannabis metabolites (limit of detection: 20 ng/mL; Medimpex United Inc), serious unstable medical illness (e.g. unstable angina, significant cardiovascular event in the prior 6 months, clinically significant cardiac conduction disorder, uncontrolled hypertension, renal failure), lifetime history of schizophrenia or bipolar disorder ascertained by medical history, current regular use of benzodiazepines or barbiturates, antihistamines, atropine, scopolamine, or other anticholinergic agents, and allergies to dronabinol or its constituents (e.g. sesame oil).

2.2. Design and intervention

Eligible, enrolled participants were randomly assigned for order to receive a single dose of 5–50 mg of dronabinol, an FDA-approved synthetic THC, in dronabinol capsules, and a single dose of identically appearing placebo capsules, on separate study visits conducted at least 7 days apart (mean days apart = 19.3; SD = 19.6). Blinding of study drug was done by over-encapsulation of dronabinol and preparation of identical placebo by the MGH Research Pharmacy. The study physicians (GP and AEE) determined the dronabinol dose, up to 50 mg, most likely to be both well-tolerated and to produce intoxication. The primary factors considered in the dosing were the degree of expected tolerance and prior adverse experiences with particular doses of THC containing products, particularly edibles. Doses were calculated for each participant based on their reported average cannabis quantity, frequency, type of cannabis and modality used, degree of intoxication (high) experienced with average dose and maximum dose, maximum dose used, history of adverse effects experienced when using cannabis, particularly oral cannabis, the dose at which adverse effects were experienced, as well as participant sex, height, weight, BMI and blood pressure. The MGH research pharmacy generated a randomization code for order and dispensed blinded drug or placebo in the dose ordered at each study visit. All members of the study staff were blind to the randomization code.

2.3. Assessments

At the screening visit, participants provided a urine sample for quantitative analysis of 11-nor-9-carboxy-tetrahydrocannabinol (THCCOOH), the main secondary THC metabolite and a widely accepted cannabis biomarker. Samples were shipped overnight to Dominion Diagnostics (Kingstown, RI) where THCCOOH levels were assayed using liquid chromatography/tandem mass spectrometry, normalized to creatinine (Huestis and Cone, 1998). A qualitative urine drug screen was performed at screening and on each study day assessing for the presence of cannabis, opioids, cocaine, amphetamines, methamphetamines, and alcohol.

Intoxication. Subjective ratings of drug effects (Drug Effects Questionnaire (DEQ; (Morean et al., 2013)) were collected at baseline and at approximately 15-min intervals for approximately 240 min post study medication at each study visit. The DEQ consisted of five questions assessing subjective drug effects, in which participants rated answers using a scale from 0 (no effects) to 100 (maximum effects). Intoxication was considered continuously (0–100). We note that while our goal was for all participants to receive a dose of THC sufficient to induce intoxication, because important factors that determine the dose required to produce intoxication (and minimize adverse effects of THC) are not possible to specify, such as the potency of THC in the cannabis used by participants in the prior month and thus the degree of tolerance, and factors related to individual differences in metabolism of THC, as well as

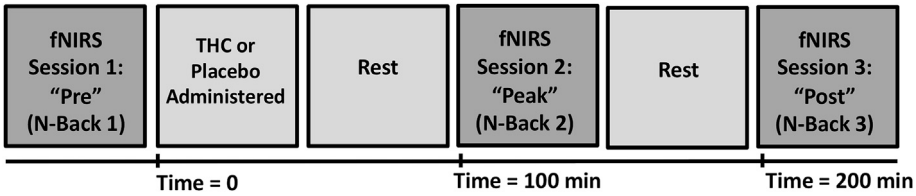

Fig. 1. Schematic diagram of study and task design. fNIRS data were collected at three time points; pre-THC/placebo administration (fNIRS Session 1), at peak intoxication (fNIRS Session 2; approximately 100 min after THC or placebo), and at post-intoxication (fNIRS Session 3; approximately 200 min after THC or placebo).

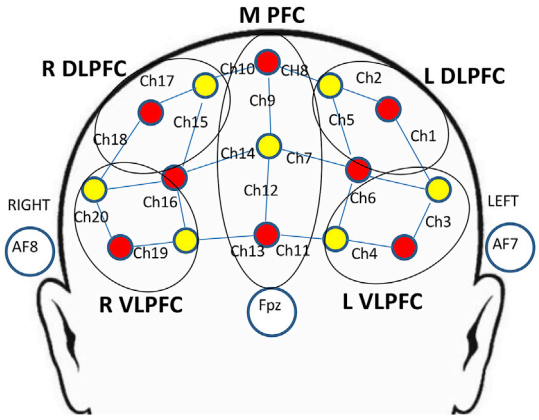

Fig. 2. Schematic arrangement of the near-infrared spectroscopy (NIRS) probe array (Top view). The CW-NIRS machine was used to measure changes in oxygenated hemoglobin (HbO) and deoxygenated hemoglobin (deoxy-Hb). The NIRS probe comprised of eight sources (red) and seven detectors (yellow) placed over the prefrontal brain region of each participant (forehead). The mid-column of the probe was placed over Fpz, with the lowest probes located along the F5-Fp1-Fpz-Fp2-F6 line, in accordance with the International 10–20 Placement System. The distance between pairs of source and detector probes was set at 3 cm. The midpoint of the source-detector distance was defined as channel (Ch) location, labeled numerically (1–20) in the above schematic. The channels were grouped into regions of interest, as illustrated in the schematic.

an IRB-approved dose limit of 50 mg THC, we expected that we would not deliver a dose of THC sufficient to produce intoxication in all participants.

Physiology. Heart rate (beats per minute; bpm) was collected pre-dose and approximately every 20 min for 240 min after THC/placebo administration.

fNIRS. Participants underwent three fNIRS scans on each of the two study days; one before THC/placebo administration ("pre"), another at approximately 100 min after THC/placebo administration ("peak"), which corresponded to the reported median peak of pharmacokinetic effects of dronabinol (Solvay Pharmaceuticals, 2004), and a final scan at approximately 200 min after THC/placebo administration ("post") (see Figs. 1 and 3). During each fNIRS scan, participants completed the 0-back and the 2-back condition of the letter N-back working memory (WM) task on a 15-inch computer screen. Letters were presented in pseudo-randomized order with a presentation time of 500 ms and an inter-stimulus-interval (ISI) of 1500 ms. During the 0-back condition, participants were instructed to press a response button whenever a letter "X" appeared on the screen. For the 2-back condition, participants were instructed to press the button whenever the presented letter was identical to the letter presented two trials prior. There were 20 target trials (true positives) in each condition across all blocks; in the 0-Back condition, there were 20 presentations of "X", and in the 2-back condition, there were 20 instances in which the presented letter was identical to the letter presented two trials prior. There were 26 distractors (non-hits) for the 0-back, and 53 distractors (non-hits) for the 2-back blocks. Starting with the 2-back, blocks alternated between the 2-back and 0-back, with a 3 s interval in between each block, in which instructions on the screen indicated whether participants should press for the 0-back or 2-back target. Each 2-back block lasted 30 s, and each 0-back block lasted 20 s. Each 2-back and 0-back block was conducted six times, resulting in a 360 s run in total. A 10s baseline period preceded the first task segment. All participants practiced the task for 1 min and were given feedback on their performance. Stimuli were generated, and responses were collected using PsychoPy (Psychophysics Software in Python).

2.4. Acquisition of fNIRS imaging data

A continuous wave-NIRS (NIRSport 8-8, NIRx, Medical Technologies LLC, New York) device was used to simultaneously acquire dual-wavelength (760 and 850 nm) near-infrared light to measure relative concentration changes in oxygenated and deoxygenated hemoglobin (HbO and HbR, respectively) (Maki et al., 1995; Yamashita, 1996) based on the modified Beer-Lambert law (Cope et al., 1988). The sampling frequency was 7.81 Hz. NIRStar software by NIRx was used to verify the signal quality before each recording. NIRS data event markers were displayed, recorded and stored on the recording PC.

The NIRS probe comprised 8 sources and 7 detectors placed over the PFC brain region of each participant (see Fig. 2 for a schematic). The mid-column of the probe was placed over Fpz, with the lowest probes located along the F5-Fp1-Fpz-Fp2-F6 line, in accordance with the International 10–20 Placement System (ldt., 2012). The center of the cap was placed over the vertex (Cz) of each participant, at a point equidistant from both nasion (Nz) and inion (Iz) and equidistant from the left and right pre-auricular (LPA and RPA) points (Jurcak et al., 2007). The distance between pairs of source and detector probes was 3 cm. The midpoint of the source-detector distance was defined as channel (Ch) location. To minimize motion artifacts in the signal, the participants were instructed to remain as still as possible.

Statistical Analysis: *Analysis of Cognitive Performance.* To examine performance accuracy in the 2-back condition of the N-back task, we converted the number of hits (the number of times a participant correctly pressed the response key when a target letter was onscreen), and false alarms (the number of times a participant pressed the response key in the absence of a target letter onscreen) into estimates of signal detection (d'; Green and Swets, 1966) using the software R (version 3.4.3; 2018).

Analysis of fNIRS Data. fNIRS analyses were conducted using the open source software, Homer2 (MGH-Martinos Center for Biomedical Imaging, Boston, MA), implemented in MATLAB (Mathworks, Natick, MA) (Huppert et al., 2009). The NIRS signal was first converted into optical density, then motion artifacts in the signal were detected and corrected by a hybrid method based on spline interpolation method and Savitzky–Golay filtering (Jahani et al., 2018). fNIRS signals were preprocessed with a high-pass filter using cut-off frequencies of 0.01 Hz to remove baseline drift and low frequency oscillations, and a 0.5 Hz low-pass filter to reduce impact of heartbeat pulsations and high frequency noise. The modified Beer-Lambert law was applied to calculate hemoglobin concentration changes with a partial pathlength factor of 6 (Cope and Delpy, 1988; Delpy et al., 1988; Boas et al., 2004). To obtain an average response to the N-back task for each of the 20 channels in each participant, the hemodynamic response function (HRF) was estimated by a general linear model (GLM) approach that used ordinary least squares. The HRF was

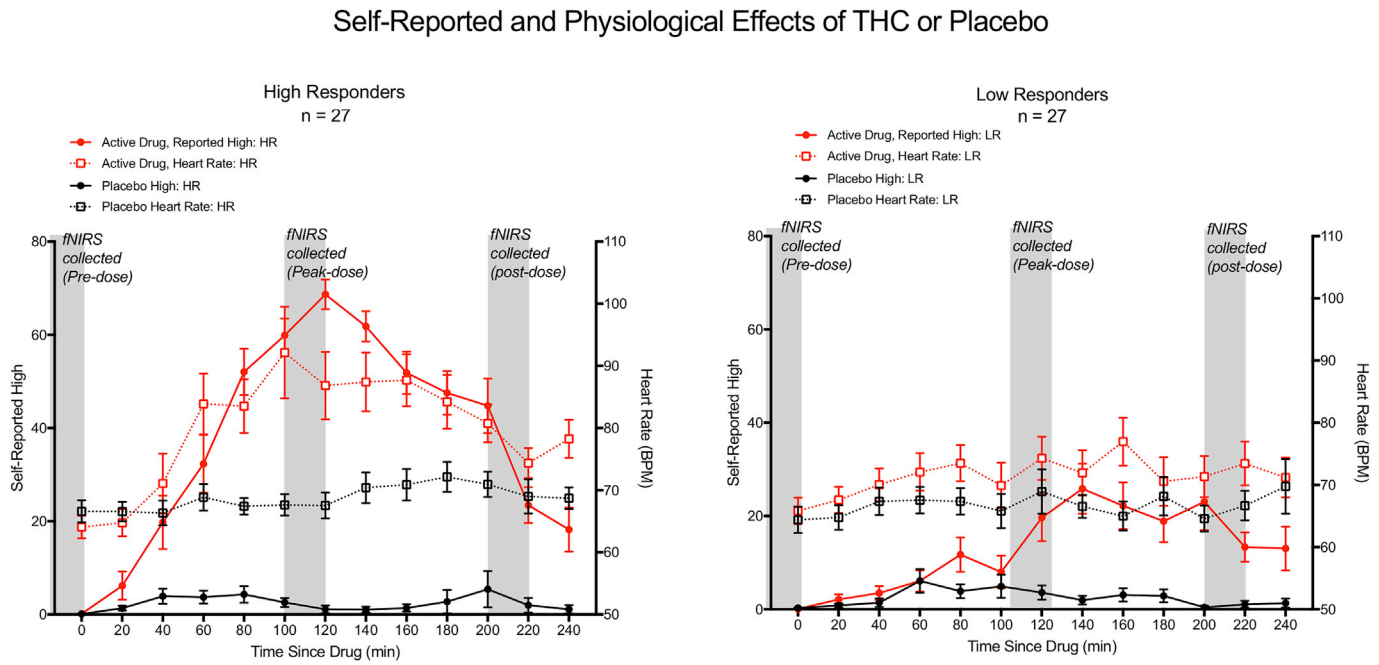

Fig. 3. Effects of dronabinol and placebo on subjective intoxication and heart rate in high (left) and low (right) responders. Approximately every 20 min, participants used a 0–100 mm visual analog scale to answer the question: "Are you high right now?", 0 mm being "Not at all" and 100 mm being "Extremely" (left y axis). Heart rate was also collected approximately every 20 min (right y axis). fNIRS sessions were initiated before THC/placebo administration, and at approximately 100 and 200 min after THC/placebo administration (shaded blocks).

modeled as a series of consecutive Gaussian functions with a standard deviation of 1 s and their means, separated by 1 s over the time range of −2 s to 40 s (Gagnon et al., 2011). We chose the mean HbO concentration change as the primary metric, as HbO concentration has been reported to provide greater SNR than HbR (Strangman et al., 2002). We chose 0–40 s as the search window because; (a) the N-Back task lasted 30s and (b) the delayed response of the hemodynamic change which usually occurs about 5–6s after the underlying neuronal activity.

We defined five ROIs based on channel location (Fig. 2). These ROIs are middle prefrontal cortex (MPFC, channels 7, 8, 9, 10, 11, 12, 13, 14); right dorsolateral prefrontal cortex (RDLPFC, channels 15, 17, 18); right ventrolateral prefrontal cortex (RVLPFC, channels 16, 19, 20); left dorsolateral prefrontal cortex (LDLPFC, channels 1, 2, 5); and left ventrolateral prefrontal cortex (LVLPFC, channels 3, 4, 6). We then performed our primary statistical analysis on the average over the following time windows for each ROI: 'pre' dose scans (e.g. pre-THC, pre-placebo), 'peak' scans at 100 min, and 'post' scans at 200 min after THC/placebo.

For all within-visit comparisons, we simply compared pre-THC/placebo HbO values to peak-THC/placebo HbO values. For between-visit comparisons, however, we aimed to control for subject-specific differences from one day to another day. Therefore, for this comparison, the HRFs of each participant were normalized at each channel to the peak magnitude of the HRF obtained from the pre-dose scan (Peng et al., 2018). This was achieved by identifying the highest value of a hemoglobin concentration increase (or the lowest value if a decrease was observed) in the pre-dose HRF within 0–40s of the N-back task. At each channel, we then divided the peak-dose scan HRFs of a subject during a single visit by the identified pre-dose HRF peak magnitude to obtain the normalized set of HRFs (Peng et al., 2018).

Analytic Strategy: We extracted (1) d' values from the N-Back task, and (2) average HbO values from the 5 ROIs in the PFC, and computed difference scores (peak-minus pre-dose). With these extracted values, we performed two separate analyses with these dependent variables. First, we computed ANOVAs to examine the effects of condition (THC, placebo), intoxication (z-scores of self-rated intoxication), and order (visit 1, visit 2), as well as their interactions. The effect of primary interest was an interaction between THC and self-rated intoxication. Effects with p-values < 0.05 were considered significant. Second, we examined correlations between the main outcome measures, change in d' and HbO, and self-reported intoxication 100 min after THC administration. Exploratory analyses via paired t-tests at each time point in the fNIRS time courses were conducted to assess differences between (1) pre-THC and peak-THC (100-min post dose), and (2) peak THC and post-THC (200-min post dose). Statistical results were corrected for multiple comparisons using Benjamini-Hochberg method with a false discovery rate of 0.05 (Benjamini and Hochberg, 1995).

3. Results

Sixty-five participants completed consent procedures, met eligibility criteria and were enrolled. Fifty-four participants (31 males, 23 females, mean age 26 ± 7.41 years) completed pre and peak (100 min) fNIRS scans following both THC and placebo, and were included in the main analyses. Of these 54 participants, 46 participants (26 males, 20 females, mean age 25.0 ± 6.51 years) also completed the fNIRS scan 200 min post dose at each visit and are included in analyses that include the post data.

HR ($N = 27$), compared to LR ($N = 27$), were younger, used cannabis on fewer occasions per day, had lower baseline state anxiety symptoms, and reported lower expectancies for relaxation and social facilitation from cannabis (see Table 1). Dose of dronabinol administered was not significantly different in HR and LR groups (HR: mean = 39.1 mg, SD = 9.8; LR: mean = 36.4 mg, SD = 14.7).

3.1. Subjective intoxication and physiological response to dronabinol

Intoxication ratings of "feeling high" increased in the overall study population following THC; the mean change from immediately prior to dosing to 100 min after dose was 42.1, SD = 30.5, t (53) = 10.14, $p < 0.001$. The HR group had an increase in intoxication ratings of 68.0 ± 14.2, whereas the LR group had an increase in intoxication ratings of only 16.1 ± 17.2, t (51) = 11.39 (Fig. 3).

Table 1
Participant characteristics at baseline grouped by self-reported high.

	Response to Dronabinol		p-value
	Low Responders (n = 27)	High Responders (n = 27)	
Demographics			
Age	28.3 (8.7)	24.0 (5.2)	0.03*
Gender (% Male, n)	55.6%, 15	59.3%, 16	0.78
Race (%, n)			
White	74.1%, 20	63.0%, 17	0.54
Black	14.8%, 4	14.8%, 4	
Other	11.1%, 3	22.2%, 6	
Ethnicity (% Hispanic, n)	25.9%, 7	22.2%, 6	0.35
Years of Education Completed	14.9 (2.4)	15.0 (2.3)	0.86
Cannabis Smoking Characteristics			
Age of Onset of Regular Cannabis Use	18.8 (6.1)	18.6 (2.6)	0.91
Frequency of use in prior 3 months (Days per week)	5.7 (1.7)	5.5 (1.5)	0.58
Frequency of use in prior 3 months (Times per day)	3.1 (2.5)	2.0 (0.93)	0.04*
Creatinine Adjusted Urine THC Concentration	316.7 (404.9)	169.4 (202.2)	0.10
CUDIT Score	12.7 (5.5)	12.8 (4.5)	0.94
Cannabis Expectancy Scores			
MEEQ			
Total	157.6 (16.2)	153.4 (13.1)	0.31
Cognitive and Behavioral Impairment	29.4 (6.7)	29.2 (7.4)	0.91
Relaxation and Tension Reduction	32.2 (3.4)	29.7 (3.9)	0.02*
Social and Sexual Facilitation	30.5 (4.8)	27.3 (4.6)	0.01*
Perceptual and Cognitive Enhancement	28.0 (4.3)	29.1 (4.0)	0.33
Global Negative Effects	13.9 (3.6)	13.1 (3.0)	0.42
Craving and Physical Effects	23.6 (3.9)	25.0 (3.1)	0.14
Alcohol Use			
AUDIT Score	7.4 (5.6)	6.1 (4.0)	0.34
Psychiatric Characteristics			
STAI			
State (Baseline)	32.4 (6.4)	29.2 (4.5)	0.04*
Trait	39.6 (9.1)	37.6 (8.5)	0.41
Lifetime Depression Dx (self-reported dx; %, n)	18.5%, 5	11.1%, 3	0.44
Any Lifetime Anxiety Dx (self-reported dx; %, n)	22.2%, 6	11.1%, 3	0.27
Dosage of Study Medication			
Dronabinol Dose	34.6 (14.7)	39.1 (9.8)	0.19

Note. All values are means and standard deviations at baseline unless otherwise noted. Unless indicated, there were no significant between-group differences in baseline characteristics in groups. Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; CUDIT, Cannabis Use Disorder Test; DX, disorder; MEEQ, Marijuana Effect Expectancy Questionnaire; STAI, State-Trait Anxiety Inventory; SD, Standard Deviation.

Heart rate also increased following THC administration, with a mean change from pre-dose to peak (100 min) of 15.5 ± 19.9 bpm, $t(53) = 5.73$, $p < 0.001$. As with self-reported intoxication, HR and LR showed different physiologic response to THC; with increased heart rate in the HR group of 24.0 ± 24.0 bpm, and in the LR group of 7.0 ± 9.1 bpm ($t(34) = 2.7$, $p = 0.011$) (Fig. 3). Increased heart rate and self-ratings of intoxication following THC were highly correlated, $R = 0.54$, $p < 0.001$.

From peak (100 min) to post (200 min) THC, intoxication ratings decreased (mean change $= 20.4 \pm 30.3$, $t(50) = -4.8$, $p < 0.001$); heart rate also decreased but the change was not significant (mean change HR $= -2.64 \pm 14.72$, $t(24) = -0.90$, $p = 0.38$; mean change LR $= -0.16 \pm 5.62$, $t(24) = -0.14$, $p = 0.89$). There were no significant changes in intoxication ratings or heart rate following placebo.

3.2. Cognitive performance

In the overall sample, there were no significant main effects of drug condition (THC/placebo) on the d' measure of cognitive performance ($p = 0.39$). There was a significant interaction between drug and self-reported intoxication ($\beta = -0.15$, $p = 0.02$), such that greater increase in intoxication ratings post THC were associated with more impaired cognitive performance from pre-to peak-THC. There was also a significant drug by order interaction in cognitive performance ($\beta = 0.15$, $p = 0.03$), indicating that there was a significant practice effect on 2-back task performance in those who received placebo during the first visit. Those who received THC on the first visit did not benefit from practice. Table S1 summarizes average 2-back hit and false alarm rates, and corresponding d' and bias estimates in the overall sample.

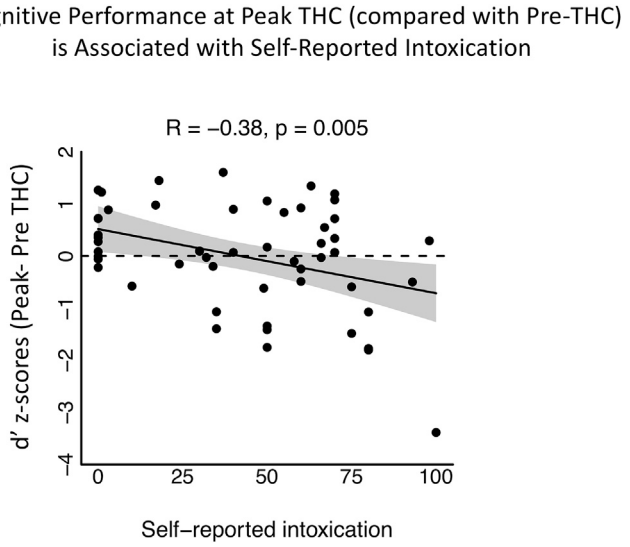

Fig. 4. Scatterplot showing the relationship between cognitive performance (d') and self-reported intoxication. Difference scores (peak – pre) were computed for performance, converted to z-scores, and then plotted against intoxication on the x-axis. The solid line shows the linear fit, while grey bands indicate the 95% confidence interval around the slope.

There was a correlation in the THC condition between self-reported intoxication and change in d' ($R = -0.38$, $p = 0.005$), indicating that following THC, those who reported greater increase in intoxication had greater degradation in performance on the task (Fig. 4). There was no correlation between intoxication ratings and d' following placebo.

3.3. fNIRS neuroimaging results

Our primary analysis compared the HbO response during the 2-back task between pre and peak THC and placebo conditions in the five ROIs: MPFC, R. DLPFC, L. DLPFC, R. VLPFC, and L. VLPFC. There was no significant main effect of THC (Fig. 5A, Table 2). In the L. and R. DLPFC and L. and R. VLPFC (4 of the 5 PFC ROIs), there was a significant drug by intoxication rating interaction, indicating that HbO response increased as levels of intoxication increased (Table 2). In Fig. 5B we illustrate, using a median split by intoxication rating, that the HR group showed significant increases in HbO 100 min after THC administration, but individuals in the LR group did not show comparable changes during peak THC (Fig. 5C). We did not detect an effect of placebo on HbO concentration in either group (Fig. 5C, D, 5E). There were no significant differences between HR and LR groups pre-dose ($p < 0.05$). Intoxication ratings were correlated with HbO increases in all regions except L. VLPFC (Fig. 6), indicating that greater HbO increases occurred when participants became intoxicated from THC.

For between-visit comparisons, in the overall sample (Fig. 7A), there were significant differences between THC and placebo peak time points in all ROIs. This effect appears to have been driven primarily by the HR subgroup (Fig. 7B), as there were few significant differences detected within the LR group (Fig. 7C).

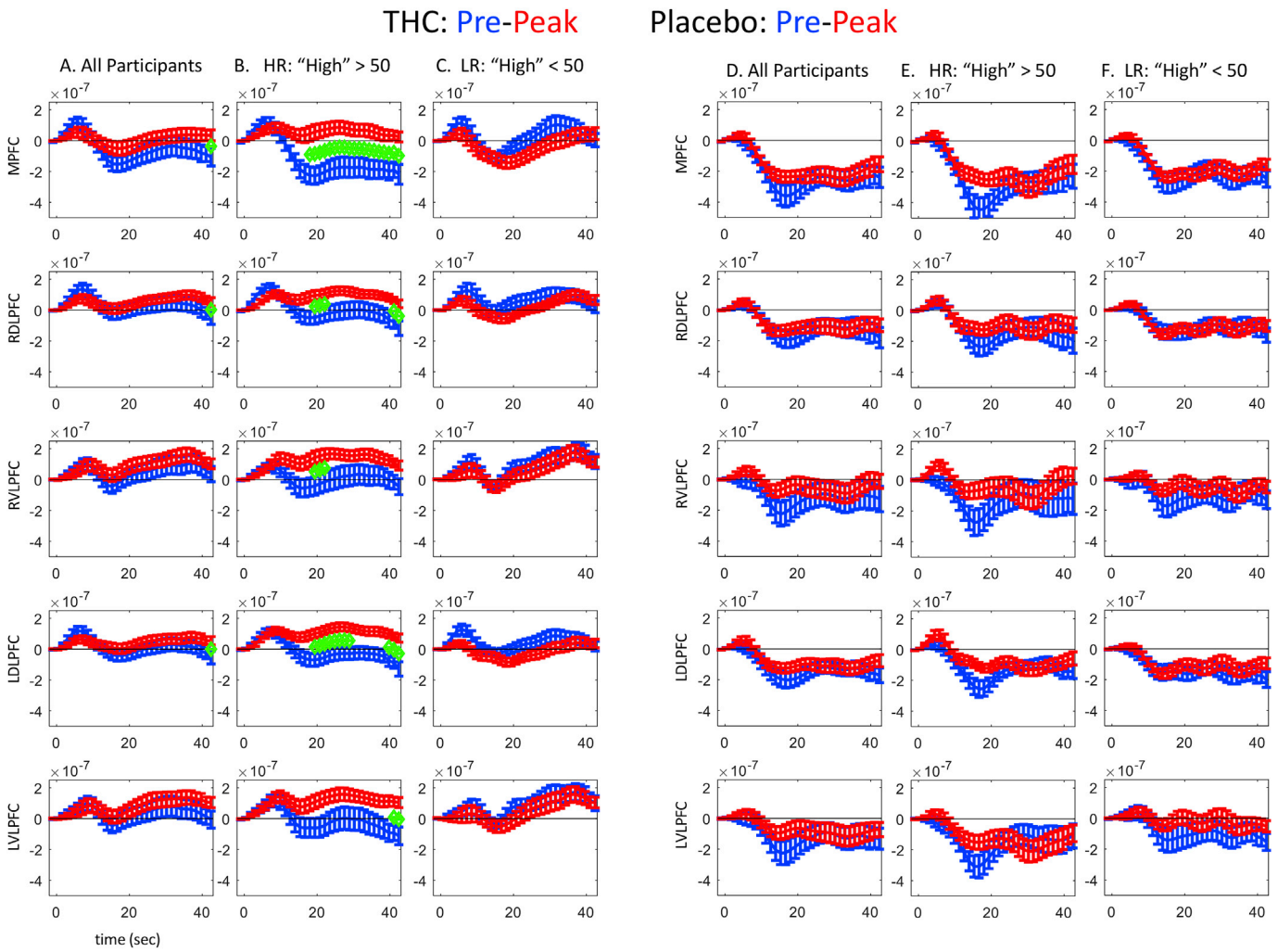

Fig. 5. HbO response at pre and peak dose in HR and LR. The time course of mean HbO changes (μM) in each ROI are plotted in all participants (4A, 4D), and by Group (HR; 4B, 4E, LR; 4C, 4F). Pre-dose HbO response is shown in blue, and peak dose is shown in red. Green lines represent single timepoints in which the group differences between pre and peak HbO were significant (FDR corrected, p-value <0.05). Error bars illustrate the standard error of the mean HRF across subjects.

Table 2
Statistical results for effects of THC, Subjective Intoxication, and Visit Order on HbO in Each Region of Interest.

Effect	R. DLPFC		L. DLPFC		MPFC		R. VLPFC		L. VLPFC	
	β	p	β	p	β	p	β	p	β	p
Main effect of SRI	−0.26	0.30	−0.32	0.20	−0.12	0.66	−0.37	0.16	−0.4	0.14
Main effect of THC	0.21	0.26	0.24	0.20	0.12	0.54	0.23	0.22	0.22	0.26
Main effect of order	0.04	0.82	−0.03	0.86	0.05	0.80	−0.09	0.66	−0.05	0.78
SRI x THC	***0.53***	***0.04****	***0.52***	***0.04****	0.42	0.10	***0.65***	***<0.01****	***0.61***	***0.02****
SRI x order	−0.29	0.24	−0.40	0.10	−0.26	0.30	−0.51	0.06	−0.48	0.08
THC x order	0.16	0.42	0.24	0.24	0.08	0.68	0.32	0.12	0.32	0.12
SRI x THC x order	0.35	0.18	0.40	0.12	0.23	0.36	0.48	0.06	0.44	0.10

Abbreviations: SRI, self-reported intoxication at peak (100 min); R, right; L, left; DLPFC, dorsolateral prefrontal cortex; MPFC, medial prefrontal cortex; VLPFC, ventrolateral prefrontal cortex. Significant results are indicated with an asterisk.

In exploratory analyses, we examined HbO responses during the post scan 200 min following THC/placebo administration, when we expected intoxication to be reduced, relative to the peak scan 100 min after THC/placebo. In four of the five ROIs examined (MPFC, R. DLPFC, R. VLPFC, and L. DLPFC), we found a significant reduction in the HbO response during post relative to peak THC (Fig. 8A). This difference was driven by the HR subgroup (Fig. 8B), as no significant differences were observed in the LR group (Fig. 8C). We did not observe any significant differences between peak and post scans during placebo runs (Fig. 8C, D, 8E).

3.4. Adverse events

Eighteen participants reported adverse events related to study medication. The most common were vomiting (4 participants), nausea, paranoia, sedation, tachycardia, anxiety, dizziness, and bradycardia/syncope (2 participants each). All were considered to be related to dronabinol.

While not considered to be adverse events, two participants had positive urine screens on the active THC day (one for cocaine, one for

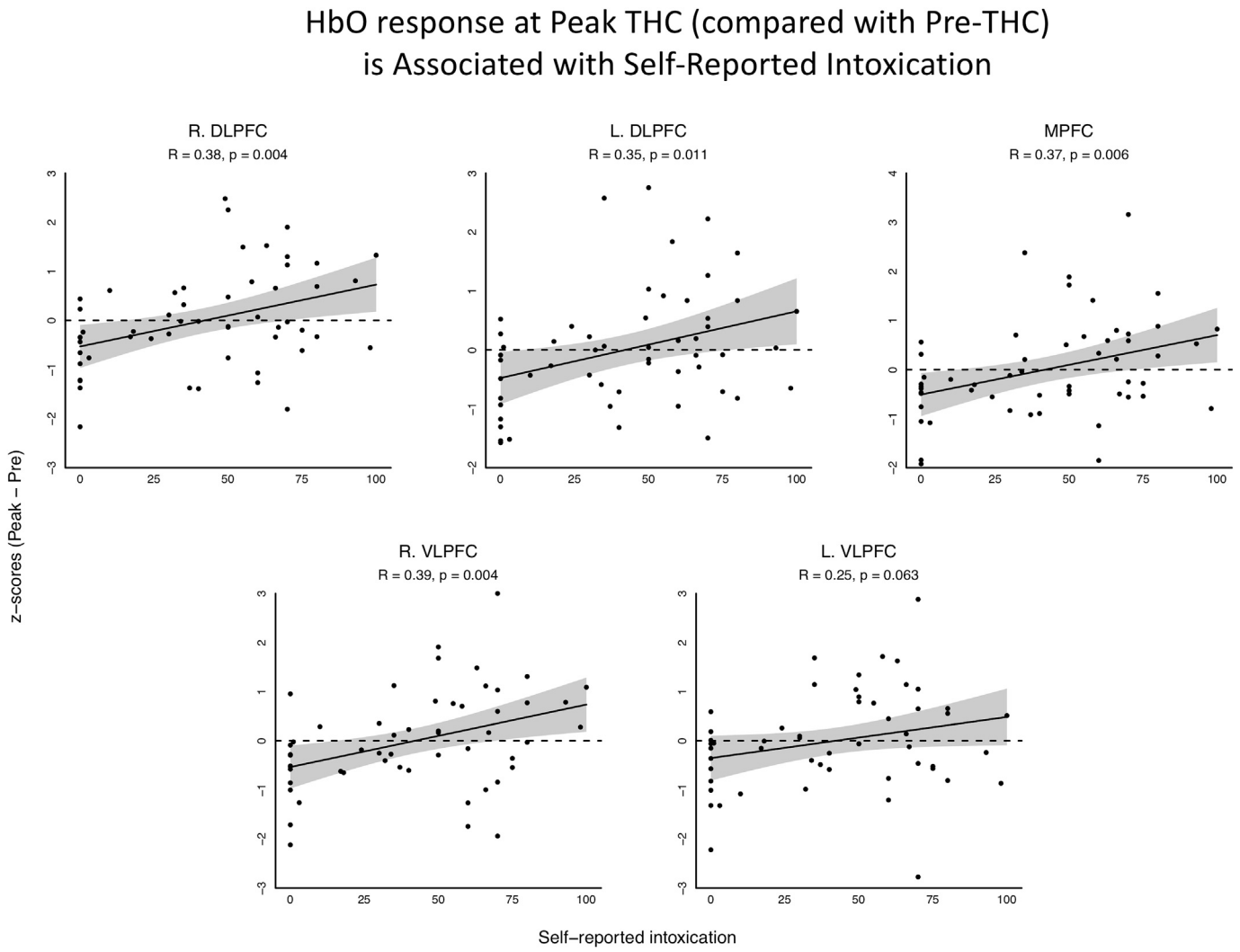

Fig. 6. Scatterplots showing the relationship between HbO response per each ROI against self-reported intoxication. Difference scores (peak – pre) for HbO response were computed, converted to z-scores, and plotted against intoxication on the x-axis. Solid lines represent linear fit, while grey bands indicate 95% confidence intervals around the slope.

amphetamines), and two participants had positive drug screens on the placebo day (one for opiates, one for amphetamines) not explained by concomitant medications. None exhibited clinical signs of intoxication and all reported use outside the window for intoxication. All other participants had negative urine screens for drugs of abuse other than cannabis on both study visit days.

4. Discussion

Intoxication from THC has been shown to produce impairment of cognitive function, including working memory, in part via binding to CB1 receptors in the PFC. Here we used fNIRS to examine the effect of THC on PFC hemodynamic response during a working memory task in a double-blind, placebo-controlled design. We observed an interaction between THC and self-reported intoxication on cognitive performance, indicating that only those who reported significant intoxication performed worse on the N-back task. We also observed increased HbO response in the PFC among participants who reported intoxication from THC. Participants on placebo and those who received THC but did not report intoxication did not show either worsening cognitive performance nor increased HbO concentration, suggesting that PFC activation could be a potential biomarker for THC intoxication.

The observed increase in PFC HbO with THC intoxication in this study is consistent with prior brain imaging studies of smoked or orally administered cannabis (Mathew et al. 1992, 1997). Further, a PET study in adult cannabis users demonstrated that THC caused global and regional increases in CBF, and these increases had stronger correlation with subjective levels of intoxication than with plasma THC concentration (Mathew et al., 2002). Task-based fMRI studies have also reported an increase in rCBF during cognitive task performance after acute THC administration (Borgwardt et al., 2008; Fusar-Poli et al., 2009), likely due to a decrease in brain efficiency with THC intoxication. Our results are consistent with the explanation that those who were more intoxicated had to expend greater effort to complete the 2-back task. Studies of various patient populations have shown enhanced activity in the brain in combination with normal levels of performance accuracy; this neurophysiological inefficiency likely indicates increased neural effort to keep performance on par (Callicott et al., 2003; Manoach, 2003). In the current study, those who received an acute dose of THC but did not report subsequent intoxication (the LR group) did not show significant physiologic effects (e.g. heart rate changes) or significant PFC activation. The observed interaction between THC administration and self-reported intoxication on PFC HbO indicates that a non-intoxicating dose of THC is not sufficient to cause significant changes in brain activity as measured by HbO concentration.

The current study extends previous literature by not only demonstrating that THC-induced PFC signal increases were positively correlated

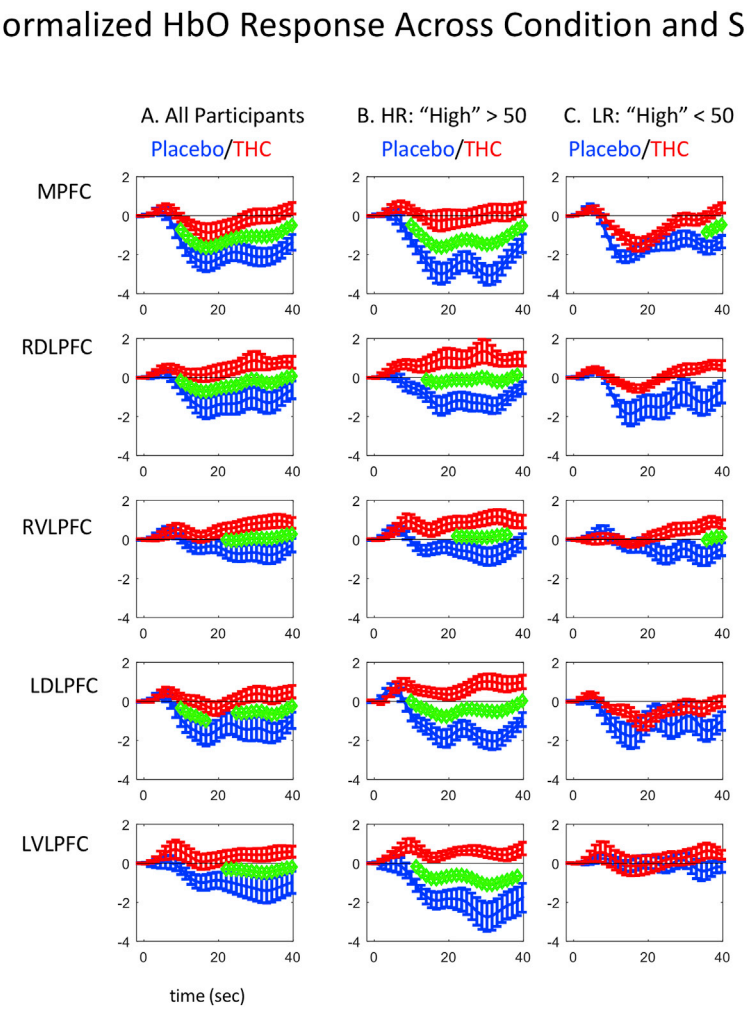

Fig. 7. Drug-Placebo (Between-Visit) Comparisons. The time courses of mean HbO changes (μM) in each ROI are plotted in all participants (7A), and by Group (HR; 7B, LR; 7C). At each channel, we divided the HRFs of a subject during a single visit during the peak scan (100 min) by the identified pre-dose scan HRF peak magnitude to obtain the normalized set of HRFs. Placebo is shown in blue, and THC is shown in red. Green lines represent single timepoints in which the group differences between pre and peak HbO were significant (FDR corrected, p-value <0.05). Error bars illustrate the standard error of the mean HRF across subjects.

with subjective measures of intoxication, but also by showing that this effect can be measured with fNIRS. We were able to demonstrate, using a simple probe design of 20 channels covering only the PFC, that increased HbO could serve as a potential biomarker of intoxication from THC. fNIRS has several advantages over other imaging modalities such as PET and functional magnetic resonance imaging (fMRI), notably that it can be used in real-world settings outside of the laboratory. Its main disadvantage is that near-infrared light pulsed into the forehead can only refracted from the tissues of the cortex, so this method cannot be used to investigate subcortical regions; however, here we show that PFC channels are sufficient to demonstrate a clear effect of THC intoxication. To date, there are no reliable biomarkers of THC intoxication, as neither THC nor THC metabolite concentration in body fluids correlates with intoxication or impairment (Schwope et al., 2012; Vandrey et al., 2017). THC metabolites remain in urine and blood for weeks after last use, and therefore, a test for cannabis metabolites in body fluids is positive long after the period of intoxication is over (Huestis et al., 1995). Though results are preliminary, this study reveals the potential of using fNIRS to objectively measure THC intoxication.

There are limitations to this study. First, it is difficult to precisely measure vascular effects of THC on cerebral blood vessels (Hollister et al., 1981; Ohlsson et al., 1980), as THC has a dilative effect on conjunctival and muscle blood vessels (Hollister et al., 1981; Ohlsson et al., 1980; Weiss et al., 1972) and prior fNIRS studies report that signal measured through fNIRS may in part arise from systemic changes that are not directly related to brain activity (Kirilina et al., 2012; Tachtsidis et al., 2008). We cannot rule out the possibility of drug-induced general vascular changes contributing at least in part to the observed HbO response during intoxication. Second, dose determination was based on detailed self-report of cannabis use. Without the information on the potency (THC content) of cannabis used by participants, it is difficult to accurately predict participants' tolerance and response to dronabinol. For this reason, some participants were expected to and did receive a dose of THC insufficient to produce intoxication. Thus, while we aimed to achieve intoxication in all participants, choosing a dose of orally administered THC to achieve the desired pharmacodynamic effects is challenging. Third, while we aimed to measure PFC activation at peak-THC, and during recovery, we determined the time interval based on published material from the MARINOL® package insert. As seen in Fig. 3, we collected data before the actual peak at 120 min, and before recovery, at 240 min. Future studies could investigate intoxication at these later time points to capture more ideal measurements. Fourth, while we chose the N-Back task based on its wide use in the fNIRS field and its ability to activate the PFC (Dommer et al., 2012; Kuruvilla et al., 2013; Aghajani and Omurtag, 2016; Aghajani et al., 2017; Vermeij et al., 2017; Tseng et al., 2018), THC affects a range of cognitive functions other than working memory (Hall and Solowij, 1998; Curran et al., 2002; D'Souza et al., 2004). Future studies can use other cognitive probes to investigate whether THC more generally increases PFC activation in those who report intoxication. Fifth, we did not collect serial measures of plasma THC concentration throughout the 240-min study procedure, which would have allowed for understanding of individual differences in oral absorption of THC and may have allowed an objective comparison of THC exposure, though plasma THC levels have been reported to not

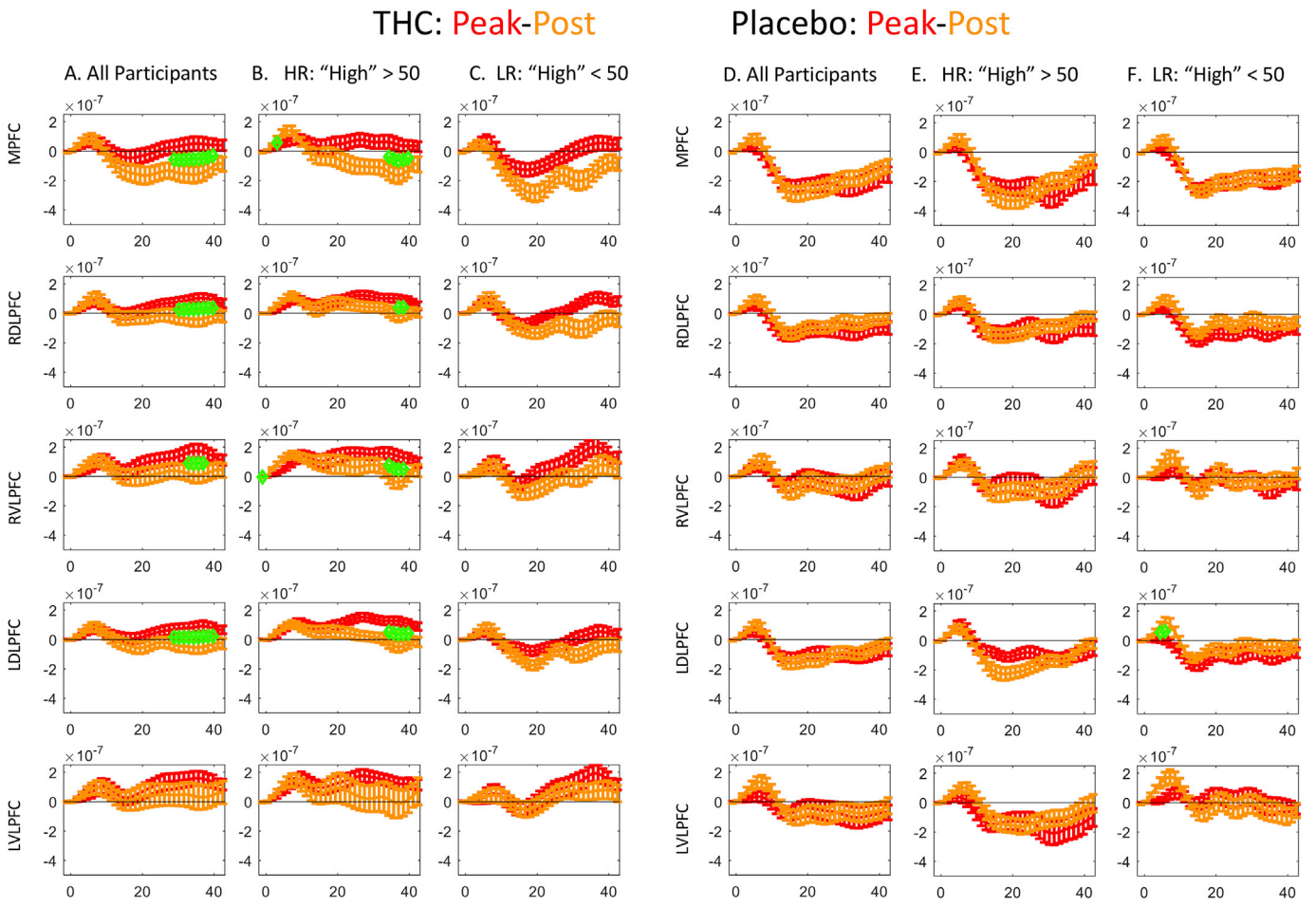

Fig. 8. HbO response at peak (100 min after THC/placebo) and post dose (200 min after THC/placebo). The time courses of mean HbO changes (μM) in each ROI are plotted in all participants (8A, 8D), and by Group (HR; 8B, 8E, LR; 8C, 8F). Peak dose is shown in red, and post is shown in orange. Green lines represent single timepoints in which the group differences between pre and peak HbO were significant (FDR corrected, p-value <0.05). Error bars illustrate the standard error of the mean HRF across subjects.

directly correlate with subjective intoxication, due to important moderating factors such as tolerance to the intoxicating effects of THC (Vandrey et al., 2017). Finally, we note that although this study was conducted in a double-blind manner for order of receiving active and placebo dronabinol, most participants who received a dose of active THC that was intoxicating for them likely realized that they had received active THC at that visit by the 100-min time point. This "unblinding" likely affected the HR group to a greater extent than the LR group, which may have in turn affected their brain response. Future studies could use an active comparator such as methylphenidate or diphenhydramine, instead of placebo THC, in order to truly rule out expectancy effects and preserve the blinding, though the impact of these medications on fNIRS measures is not well known.

In conclusion, this study demonstrates that acute THC-induced intoxication causes significantly greater HbO concentration increase in the PFC than placebo or acute THC at similar doses not associated with significant intoxication. While we cannot rule out that these effects may be generally associated with intoxication, rather than from THC specifically, these results are consistent with rCBF findings in the PET literature following THC administration. Significant correlations between HbO increases and subjective intoxication suggest that PFC increases are specific to THC intoxication, rather than THC administration alone. This is important because PFC activation, measured by HbO response, may be a biomarker of THC intoxication. An important next step in this line of research is to begin to test how combinations of drugs that are commonly used together, such as THC and alcohol or opiates, affect PFC activation.

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Authors' contributions

Conceived and designed the experiments: JMG, AEE. Performed the experiments: HB, EM, NL. Oversaw clinical aspects: GP, AEE. Analyzed the data: MAY, JMG, KP. Wrote the paper: JMG, AEE, MAY, RMS. All authors have approved the final article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2019.05.012.

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