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Modulation of acute effects of delta-9-tetrahydrocannabinol on psychotomimetic effects, cognition and brain function by previous cannabis exposure

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Abstract
Cannabis use has been associated with psychosis and cognitive dysfunction. Some evidence suggests that the acute behavioral and neurocognitive effects of the main active ingredient in cannabis, (−)-trans-Δ9-tetrahydrocannabinol (Δ9-THC), might be modulated by previous cannabis exposure. However, this has not been investigated either using a control group of non-users, or following abstinence in modest cannabis users, who represent the majority of recreational users. Twenty-four healthy men participated in a double-blind, randomized, placebo-controlled, repeated-measures, within-subject, Δ9-THC challenge study. Compared to non-users (N=12; <5 lifetime cannabis joints smoked), abstinent modest cannabis users (N=12; 24.5±9 lifetime cannabis joints smoked) showed worse performance and stronger right hemispheric activation during cognitive processing, independent of the acute challenge (all $P \leq 0.047$). Acute Δ9-THC administration produced transient anxiety and psychotomimetic symptoms (all $P \leq 0.02$), the latter being greater in non-users compared to users (P=0.040). Non-users under placebo (control group) activated specific brain areas to perform the tasks, while deactivating others. An opposite pattern was found under acute (Δ9-THC challenge in non-users) as well as residual (cannabis users under placebo) effect of Δ9-THC. Under Δ9-THC, cannabis users showed brain activity patterns intermediate between those in non-users under placebo (control group), and non-users under Δ9-THC (acute effect) and cannabis users under placebo (residual effect). In non-users, the more severe the Δ9-THC-induced psychotomimetic symptoms and cognitive impairments, the more pronounced was the

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neurophysiological alteration (all $P \leq 0.036$). Previous modest cannabis use blunts the acute behavioral and neurophysiological effects of Δ9-THC, which are more marked in people who have never used cannabis.

1. Introduction

Cannabis is widely used, with approximately 200 million users worldwide (National Academies of Sciences and Medicine, 2017). Both cannabis (Henquet et al., 2005; Skinner et al., 2011; van Gastel et al., 2012; Colizzi and Murray, 2018) and its key psychoactive ingredient delta-9-tetrahydrocannabinol (Δ9-THC) (Bhattacharyya et al., 2012a; Bhattacharyya et al., 2009; D'Souza et al., 2004) can induce psychotic symptoms and trigger the onset of psychosis in vulnerable individuals (Colizzi et al., 2015a; Colizzi et al., 2015b; Moore et al., 2007; Morrison et al., 2015). Moreover, cannabis use can exacerbate psychotic symptoms (Ouellet-Plamondon et al., 2017; Schoeler et al., 2016a; Seddon et al., 2016), increase risk of non-remission (Colizzi et al., 2016a) and cause relapse (Patel et al., 2016; Schoeler et al., 2016b) in patients with established psychosis in a dose-dependent manner (Schoeler et al., 2016c).

Cannabis use has also been associated with cognitive impairments in similar domains to those where impairments are seen in patients with schizophrenia, such as memory and attention (Ganzer et al., 2016; Solowij and Michie, 2007). However, there is inconsistency with regard to the precise nature and extent of the effects of cannabis on human cognition (Bolla et al., 2002; Jockers-Scherubl et al., 2007; Pope et al., 2001; Solowij et al., 2002; Colizzi and Bhattacharyya, 2017). Long-lasting detrimental effects of cannabis use on cognition are still debated and appear to be more prominent on specific cognitive domains, such as verbal and visual memory, as suggested by meta-analytic evidence (Grant et al., 2003; Schoeler et al., 2016d). Results from experimental studies investigating the acute neurocognitive effects of Δ9-THC are more consistent and suggest that Δ9-THC administration in healthy volunteers acutely impairs several cognitive domains, including verbal (Curran et al., 2002; D'Souza et al., 2004; Ranganathan and D'Souza, 2006) and working memory (D'Souza et al., 2004; Ranganathan and D'Souza, 2006) and inhibitory control (McDonald et al., 2003; Ramaekers et al., 2009; Ramaekers et al., 2006; Weinstein et al., 2008a) processing. Additional evidence from neuroimaging studies suggests that acute Δ9-THC administration disrupts the neurophysiological underpinnings of a variety of cognitive processes that are also impaired in patients with psychosis, including verbal memory (Bhattacharyya et al., 2012a; Bhattacharyya et al., 2009), inhibitory control processing (Bhattacharyya et al., 2015a; Hester et al., 2009; Weinstein et al., 2008b), emotional processing and attentive salience (Bhattacharyya et al., 2012b; Bhattacharyya et al., 2015b; Bhattacharyya et al., 2010), and visual and auditory processing (Bhattacharyya et al., 2010; Winton-Brown et al., 2011).

Previous cannabis exposure has been associated with less marked effects of acute Δ9-THC administration on cognitive functioning (memory) as well as behavioral measures (observed and experienced psychiatric symptoms) and electrophysiological (gamma (γ)-band oscillations and P300 wave), neurochemical ((brain-derived neurotrophic factor (BDNF)), and neuroendocrine markers (cortisol) (Cortes-Briones et al., 2015; D'Souza et al., 2008a; D'Souza et al., 2008b; D'Souza et al., 2012; Ramaekers et al., 2009; Ranganathan et al., 2009; Schoeler and Bhattacharyya, 2013). While this may suggest a development of tolerance to the effects of Δ9-THC in cannabis users (Gonzalez et al., 2005; Hirvonen et al., 2012; Jones et al., 1981), the interpretation of these findings is challenging in light of methodological heterogeneity between the studies in terms of pattern of cannabis use and abstinence period prior to assessment. Some studies conducted exploratory analyses of the association between recent exposure to cannabis (in 30 days before study participation) and electrophysiological measures within a single group of subjects with a wide variation in the extent of previous cannabis exposure in terms of lifetime use (from <5 to >1000 times lifetime), frequency of use during periods of heaviest use (from ≤ 1 per year to daily), and in recent times (from 0 to 29 days in the last month) (Cortes-Briones et al., 2015; D'Souza et al., 2012). On the other hand, a study that compared 2 separate groups did not include a control group of non-users, comparing heavy (on average, 340 occasions in the last year and 6.2 years of history of exposure) and occasional cannabis users (on average, 55 occasions in the last year and 7.4 years of history of exposure) with no abstinent period prior to assessment (Ramaekers et al., 2009). Other studies compared frequent users ($\geq$ 100 times lifetime) with a history of sustained and/ or daily use and with no or modest ($\geq$ 72 h to $<$ 1 month) abstinence period prior to assessment, and controls with a wide range of previous cannabis exposure in terms of frequency ($<$ 5 to $>$ 100 times lifetime) and either a relatively short ($<$ 1 month) or a heterogeneous abstinence period ($>$ 1week and $<$ 10 years) (D'Souza et al., 2008a; D'Souza et al., 2008b; Ranganathan et al., 2009). Hence, whether modest previous exposure to cannabis, that reflects the typical pattern of use of the majority of recreational cannabis users (National Academies of Sciences and Medicine, 2017), affect the acute cognitive and psychotomimetic effects of its key psychoactive ingredient (Δ9-THC) as well as the neurophysiological effects that may underlie these behavioural effects, remains unclear.

We sought to address this issue by systematically investigating how the acute behavioural and neurophysiological effects (as indexed using functional magnetic resonance imaging; fMRI) of Δ9-THC differ between non-users and abstinent cannabis users with modest previous cannabis exposure who have a negative result on urine drug screen.

Employing a placebo-controlled acute pharmacological challenge design in conjunction with fMRI, we examined the following hypotheses: 1) modest cannabis use would be

associated with residual symptomatic, cognitive, and underlying neurophysiological effects measured using fMRI blood oxygen level-dependent haemodynamic response (BOLD) signal; 2) acute Δ9-THC effects on symptomatic, cognitive, and neurophysiological signals that underpin its effects on key cognitive processes affected by cannabis use would be more marked in non-users than users.

2. Experimental procedures

Data presented here are based on that acquired during a previous experimental study, the methods of which have already been reported in detail (Bhattacharyya et al., 2015a; Bhattacharyya et al., 2009). In brief, this study employed a double-blind, randomized, placebo-controlled, repeated-measures, within-subject design, with counterbalanced order of drug administration (Δ9-THC, placebo), using an established protocol (Bhattacharyya et al., 2012a; Bhattacharyya et al., 2010). Randomization was performed using a Random Number Generator freely available online with blocks of size 6. The two study sessions were separated by at least one-month interval. Following drug administration, study participants were imaged using fMRI (1.5 T scanner).

In the present manuscript, we focus on the effects of previous cannabis exposure on the acute effects of Δ9-THC, which have not been reported before.

2.1. Study protocol

Two hours before each session, study participants had a light standardized breakfast after an overnight fast. Also, participants were advised to get at least 6 h sleep the night before each session. One hour before imaging, they were given a gelatin capsule containing Δ9-THC (10 mg, approximately 99.6% pure; THC-Pharm, Frankfurt, Germany), or flour (placebo). A dose of 10 mg of Δ9-THC was used, as previous work has suggested that this dose can induce detectable effects on cognitive processes without causing marked psychotic or anxiety reactions that may affect the ability of participants to complete the imaging component of the study (Chesher et al., 1990; Koethe et al., 2006; Leweke et al., 1999). Some previous studies have used even higher doses of Δ9-THC ($\geq$ 15 mg), however these investigations aimed at assessing the effects of Δ9-THC administration in individuals with cannabis dependence (Fischer et al., 2014) or the deposition of cannabinoids in human hair following controlled administration of Δ9-THC (Huestis et al., 2007). All subjects had a negative urinary drug screen for amphetamines, benzodiazepines, cocaine, opiates, and Δ9-THC, tested before each session using immunometric assay kits. They were asked to refrain from smoking for 4 h, to take caffeine for 12 h and alcohol for 24 h prior to each scan session. Also, subjects were advised to abstain from using any substance throughout the duration of the study.

2.2. Subjects

Thirty-six healthy, English-speaking, right-handed males participated in this study. Participants were recruited using local advertisements and a list of healthy participants who had agreed to be contacted for research studies. All except 3 (1 Chinese and 2 Sri-Lankan) of the volunteers were white Europeans. Demographic information such as age (Mean $\pm$ SD; age: 26.0 $\pm$ 5.6 years) and level of education (17.1 $\pm$ 4.2 years) was recorded and Intelligence Quotient (IQ, 97.7 $\pm$ 6.0) was also measured using the National Adult Reading Test (Schlosser and Ivison, 1989) (NART). All subjects gave written, informed consent, and completed all of the components of the study. Personal or family history of psychiatric illness in first-degree relatives represented an exclusion criterion in addition to the standard MRI exclusion criteria. None of the subjects included in the study had used more than 21 units/week of alcohol on a regular basis (1 unit = 8 g of pure alcohol). Nine subjects had lifetime history of smoking cigarettes, two of them smoked $>$ 10 cigarettes/ day, and only one subject smoked at that level at the time of the study (number of cigarettes smoked/day; M $\pm$ SD, 1.2 $\pm$ 3.2; Range: 0–15).

2.3. Lifetime cannabis and other substance use

Cannabis as well as other substance use was assessed using the Structured Clinical Interview for DSM Disorders (SCID) and the Addiction Severity Index (McLellan et al., 1992). Lifetime cannabis exposure was indexed as the total number of cannabis joints used in their lifetime at the time of taking part in the study. In accordance with the World Health Organization (WHO) standards (Haro et al., 2006) lifetime cannabis use less than 5 times was considered negligible use and subjects reporting negligible use were categorised as non-users (NU). Out of the total cohort of 36 subjects, 12 subjects qualified as NU, representing the lower tertile of the sample in terms of lifetime cannabis use. When testing for the effects of Δ9-THC on symptoms, cognition, and brain function as a function of lifetime cannabis use, this lower tertile (NU; cannabis joints smoked: 3.5 $\pm$ 1, range: 2–5; age: 25.3 $\pm$ 4.1 years; level of education: 16.0 $\pm$ 3.5 years; IQ, 97.5 $\pm$ 7.1; tobacco users: 4 subjects) of the sample was compared with the upper tertile of the sample in terms of lifetime cannabis use (cannabis users, CU; cannabis joints smoked: 24.5 $\pm$ 9; range: 14–40; age: 27.2 $\pm$ 6.9 years; level of education: 19.0 $\pm$ 5.7 years; IQ, 98.2 $\pm$ 7.9; tobacco users: 3 subjects), for a more differentiated analysis (N = 24). This pattern of lifetime cannabis use is comparable with that of recreational cannabis users ($\geq$ 10 times) who have participated in previous investigations of the acute effects of Δ9-THC on behavioral measures (McDonald et al., 2003). This approach of splitting the total sample into upper and lower tertiles in terms of lifetime cannabis use was adopted to ensure that the two groups (CU and NU) were sufficiently different in terms of previous cannabis exposure such that the modulatory effects of modest previous exposure on acute effects may be investigated. Subjects were asked not to have used cannabis in the 3 months before the first scan. We did not include individuals with heavier patterns of cannabis use in order to avoid the confounding effects of withdrawal symptoms which have been reported following the cessation of heavy cannabis use (Budney et al., 2003). Hereafter, unless otherwise specified, subjects will refer to only these 24 participants. However, for the sake of completeness, the acute behavioral and symptomatic effects of Δ9-THC on the entire sample (N = 36) are also reported.

The same WHO criterion (Haro et al., 2006) adopted for cannabis use was used to screen for other substance use in terms of exclusion criterion. None of the subjects included in this study had used any other substance more than 5 times in their life.

2.4. Whole-blood Δ9-THC levels and physiological measures

Blood samples were obtained from an indwelling intravenous line in the nondominant arm immediately before and at 1, 2, and 3 hours after drug administration. Whole-blood drug levels were measured using commercially available agents (Tricho-Tech, Cardiff, England). Heart rate and blood pressure were monitored via a digital recorder and an automated arm cuff.

2.5. Psychopathological measures

Immediately before and at 1, 2, and 3 h after drug administration, psychopathological ratings were recorded by an expert clinical

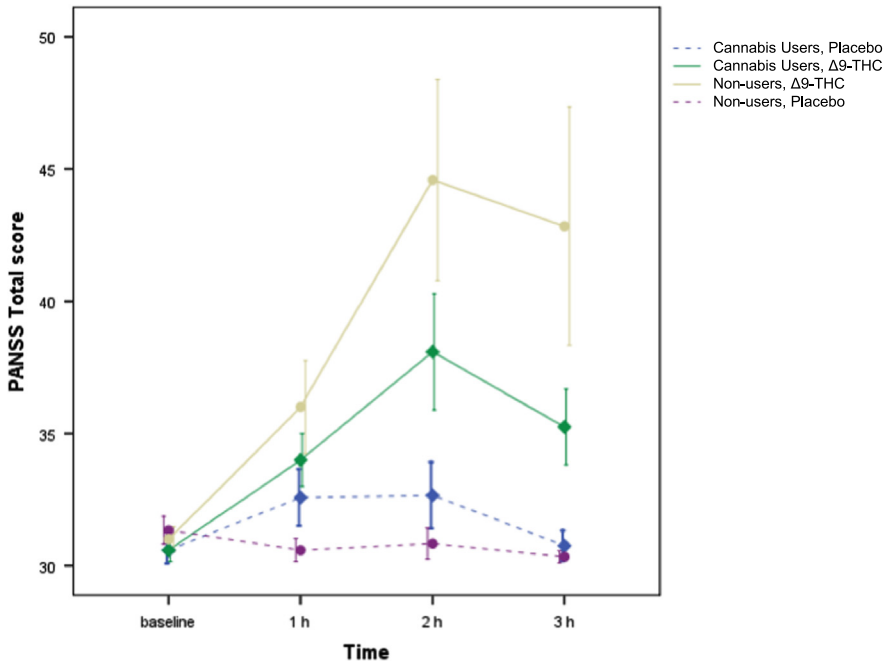

Fig. 1 Acute effect of Δ9-THC in cannabis users and non-users. Δ9-THC, (−)-trans-Δ^9-tetrahydrocannabinol; PANSS, Positive and Negative Syndrome Scale; h, hour; Dashed line, Placebo; Solid line, Δ9-THC; Circle marker, Non-users; Diamond marker, Cannabis-users.

researcher using the Positive and Negative Syndrome Scale (Kay et al., 1987) (PANSS) and the State-Trait Anxiety Inventory (Guillen-Riquelme and Buela-Casal, 2014) (STAI), in order to assess psychotic and anxiety symptoms. As measures of sedation and intoxication, the Visual Analog Mood Scale (Folstein and Luria, 1973) (VAMS), and Analog Intoxication Scale (Mathew et al., 1992) (AIS) were also administered. For the symptomatic effects of Δ9-THC, the area under the curve (AUC) of effects versus time was first calculated by the trapezoidal rule and was contrasted with the placebo condition.

2.6. Cognitive and imaging paradigms

Based on the consistent and replicated evidence that cannabis exposure might affect verbal memory and learning (Grant et al., 2003; Schoeler and Bhattacharyya, 2013), as well as inhibitory control processing (Bhattacharyya et al., 2015a; McDonald et al., 2003; Ramaekers et al., 2006; Tapert et al., 2007), during each imaging session participants performed: 1. a verbal paired associate learning task comprising 3 conditions ('encoding', 'recall', and 'baseline'), with stimuli presented visually in blocks (Schlosser and Ivison, 1989; Warner et al., 1987); 2. a response inhibition task, requiring either the execution ('Go') or the inhibition ('No-Go') of a motor response depending on the visual presentation of stimuli (Borgwardt et al., 2008). fMRI data was analysed using a non-parametric factorial analysis of variance (XBAM version 4.1), in order to test for the main effects as well as the interaction of lifetime cannabis exposure and drug administration on brain function, contrasting whole-brain activation while performing the tasks in CU with that obtained from NU. Further description of the cognitive tasks along with details about the imaging data acquisition and analysis is reported in Supplementary methods.

2.7. Ethics

The study was approved by the Joint South London and Maudsley (SLaM) and Institute of Psychiatry, Psychology & Neuroscience (IoPPN) National Health Service Research Ethics Committee, and the investigators had a license to use Δ9-THC for research purposes. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

3. Results

There were no significant differences between the CU (N = 12) and NU (N = 12) groups in terms of demographic variables, proportion of tobacco users, Δ9-THC blood levels, and physiological measures (all $P > 0.1$; Supplementary results).

3.1. Psychopathological measures

3.1.1. Acute effect of Δ9-THC

As expected, administration of Δ9-THC was associated with the acute induction of psychotic symptoms (area under the curve, AUC, PANSS positive symptoms subscale, $t = 3.76$, $P = 0.01$; AUC PANSS negative symptoms subscale, $t = 2.87$, $P = 0.009$; AUC PANSS general symptoms subscale, $t = 4.27$, $P < 0.001$; AUC PANSS total score, $t = 4.30$, $P < 0.001$) in the present study sample as in the total cohort (Supplementary results). Δ9-THC also induced a significant acute increase in anxiety (AUC STAI scale, $t = 2.51$, $P = 0.02$) and intoxication (AUC AIS, $t = 5.85$, $P < 0.001$) and a trend-level increase in mental (AUC VAMS mental sedation subscale, $t = 1.89$, $P = 0.07$) but not physical sedation (AUC VAMS physical sedation subscale, $P > 0.1$).

3.1.2. Acute effect of Δ9-THC clustered by lifetime cannabis exposure

Under placebo, CU and NU did not differ in psychopathological ratings ($P > 0.1$). However, as hypothesized, the effect of Δ9-THC on psychotic symptoms was more

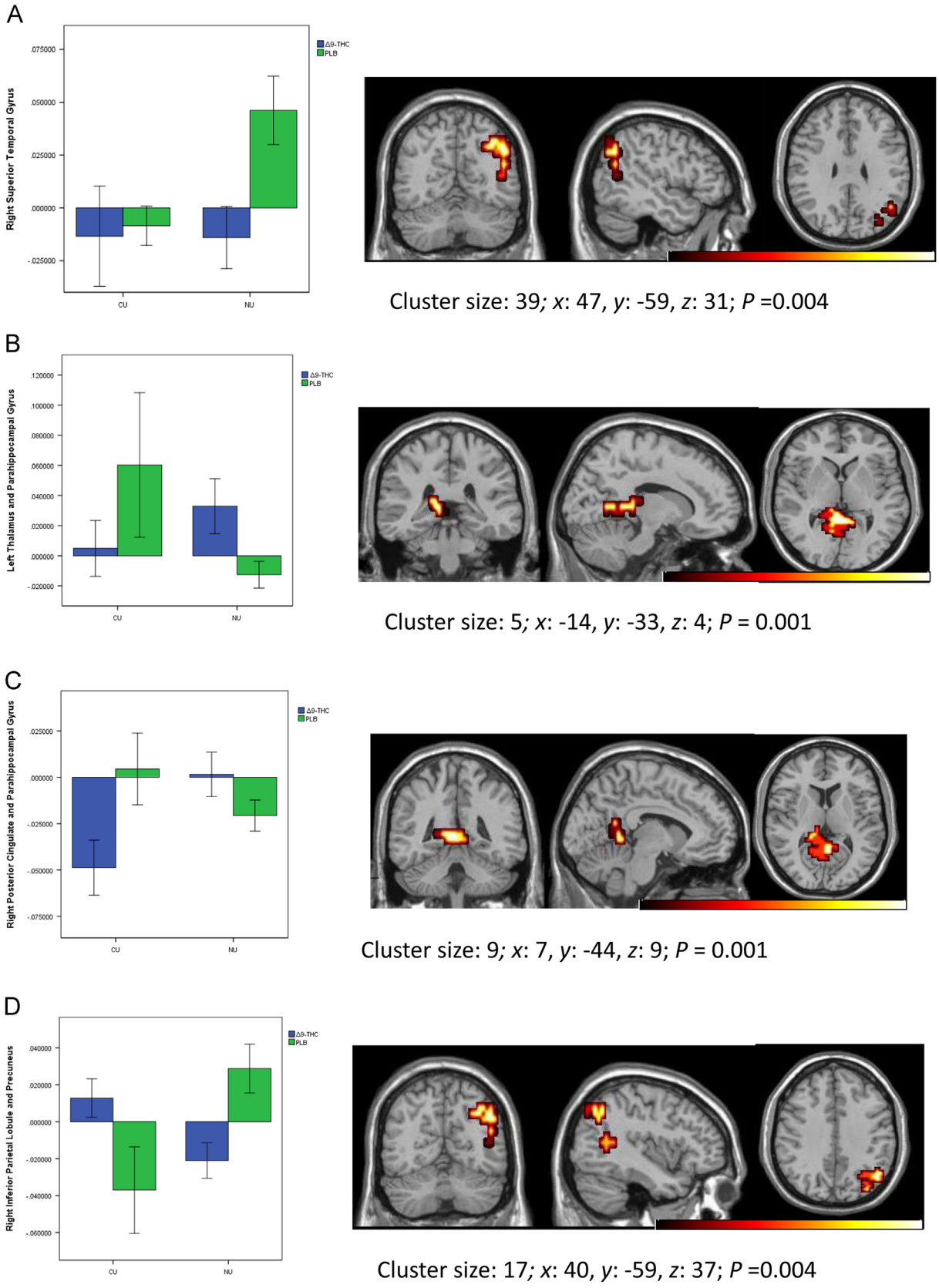

Fig. 2 Interaction between Δ9-THC administration and lifetime cannabis exposure on brain function during verbal learning encoding. 'Encoding' condition contrasted with 'baseline' condition; Δ9-THC, (−)-trans-Δ9-tetrahydrocannabinol; PLB, Placebo; CU, Cannabis users; NU, Non-users; Y-axis displays SSQ statistic; the cluster size refers to the specific brain area and is part of a larger cluster encompassing different brain areas (A, size: 56; B, size: 81; C, size: 81; D, size: 56).

pronounced in NU compared to CU, with a significantly higher AUC PANSS total score ($F = 4.77$, $P = 0.040$; Fig. 1) and a trend towards significance for all of the AUC PANSS subscales (NU > CU; AUC PANSS positive symptoms subscale; $F = 3.91$, $P = 0.061$; AUC PANSS negative symptoms subscale; $F = 4.08$, $P = 0.056$; AUC PANSS general symptoms subscale; $F = 4.11$, $P = 0.055$). There was no significant ($P > 0.1$) difference in Δ9-THC-induced symptoms of anxiety or sedation between CU and NU. In addition, there was no significant effect of order of drug administration and no interaction between the effects of drug and order of administration on any of the psychopathological measures.

3.2. Behavioral measures

3.2.1. Verbal paired associate learning task performance

As in the total cohort (Supplementary results), there was no significant effect of Δ9-THC on performance during the learning task as measured by recall score ($P > 0.1$) in the combined CU and NU sample. However, there was progressive improvement in word recall with repeated presentation of word pairs across encoding blocks for both drug conditions ($F = 8.21$, $P < 0.001$), with no significant effect of Δ9-THC on this repetition-related improvement ($P > 0.1$). Compared to NU, during the placebo condition CU showed slower learning as indexed by slower improvement in recall score across repeated blocks ($F = 4.17$, $P = 0.047$). This effect was no longer significant during the Δ9-THC condition. There was also no significant effect of order of drug administration and no interaction between the effects of drug and order of administration on recall score.

3.2.2. Response inhibition (Go/No-Go) task performance

There was a higher frequency of inhibition errors under Δ9-THC (6.4%) than under placebo (1.9%; $\chi^2 = 14.7$; $P < 0.001$) in the current study sample similar to the total cohort (Supplementary results). However, while NU made significantly more errors under the influence of Δ9-THC compared to placebo (Δ9-THC: 6.25%, placebo: 0.35%; $P < 0.001$), in CU the Δ9-THC-induced increase in frequency of inhibition errors was less pronounced (Δ9-THC: 6.6%, placebo: 3.5%; $\chi 2 = 2.94$; $P = 0.09$). Compared to NU, during the placebo condition CU reported ten times more inhibition errors ($P = 0.01$). This effect was no longer significant during the Δ9-THC condition, with a similar pattern in terms of frequency of inhibition errors in CU and NU ($P > 0.1$). As a result, the Δ9-THC-induced increase in inhibition errors was greater in NU than CU ($P = 0.03$). There was no significant effect of order of drug administration and no interaction between the effects of drug and order of administration on frequency of inhibition errors.

3.3. fMRI results

3.3.1. Verbal learning task

3.3.1.1. Effects of Δ9-THC administration and lifetime cannabis exposure and their interaction. Factorial ANOVA revealed a main effect of lifetime cannabis exposure on activation during encoding, such that CU engaged the right caudate and parahippocampal gyrus more than NU (Fig. S4). There was no significant main effect of Δ9-THC on brain activation during encoding. However, there was an interaction between Δ9-THC administration and lifetime cannabis exposure (Table S1). Under the placebo condition, encoding of word pairs was associated with activation in the right superior temporal gyrus in NU individuals (control group), whereas this region was deactivated in NU under the Δ9-THC condition, and in CU under both the Δ9-THC and placebo conditions (Fig. 2A). Moreover, while NU individuals under the placebo condition deactivated the parahippocampal gyrus bilaterally, the left thalamus, and the right posterior cingulate, both NU under the Δ9-THC condition and CU under the placebo condition activated these areas. In addition, under the Δ9-THC condition, there was only weak left parahippocampal and thalamic activation in CU, and deactivation in the right parahippocampal gyrus and posterior cingulate, similar to NU under placebo (Fig. 2B and C). Under the placebo condition NU activated the right inferior parietal lobule and precuneus, while both NU under the Δ9-THC condition and CU under the placebo condition deactivated this area. Intriguingly, once again CU under the Δ9-THC condition activated the right inferior parietal lobule and precuneus, showing a pattern of activation similar to NU under placebo (Fig. 2D).

Factorial ANOVA during recall failed to show significant interaction between lifetime cannabis exposure and Δ9-THC administration (Supplementary results).

3.3.1.2. Association between psychopathological measures, behavioral performance, and brain activation during verbal learning. Due to the established left-lateralized pattern of parahippocampal activation during encoding of verbal stimuli (Chua et al., 2007; Powell et al., 2005; Rosazza et al., 2009) and evidence here that the effect of Δ9-THC in this brain area differs between CU and NU, a correlation analysis was conducted to examine the relationship between brain activity in the left parahippocampal gyrus and behavioral measures that were also different between CU and NU, in particular AUC PANSS total score and improvement in recall score across repeated blocks (learning). In the NU group, the Δ9-THC-induced change in left parahippocampal activation (Δ9-THC minus placebo) positively correlated with the severity of psychotic symptoms induced by Δ9-THC (rS: 0.61; $P = 0.036$; Fig. 3A) as well as with its effects on learning (Δ9-THC minus placebo; r: 0.63; $P = 0.028$; Fig. 3B). These correlations were not observed in the CU group. Further, post-hoc testing indicated that the relationship between the effect of Δ9-THC on left parahippocampal gyrus engagement was specific to psychotic-like symptoms under its influence, as such a relationship did not exist between the engagement of the left parahippocampal gyrus induced by Δ9-THC and its effect on the severity of intoxication, sedation, and anxiety symptoms.

3.3.2. Response inhibition (Go/No-Go) task

3.3.2.1. Effects of Δ9-THC administration and lifetime cannabis exposure and their interaction. Factorial ANOVA revealed a main effect of lifetime cannabis exposure on brain function during inhibitory control processing, such that CU engaged the right postcentral gyrus extending to the inferior parietal lobule and superior temporal gyrus

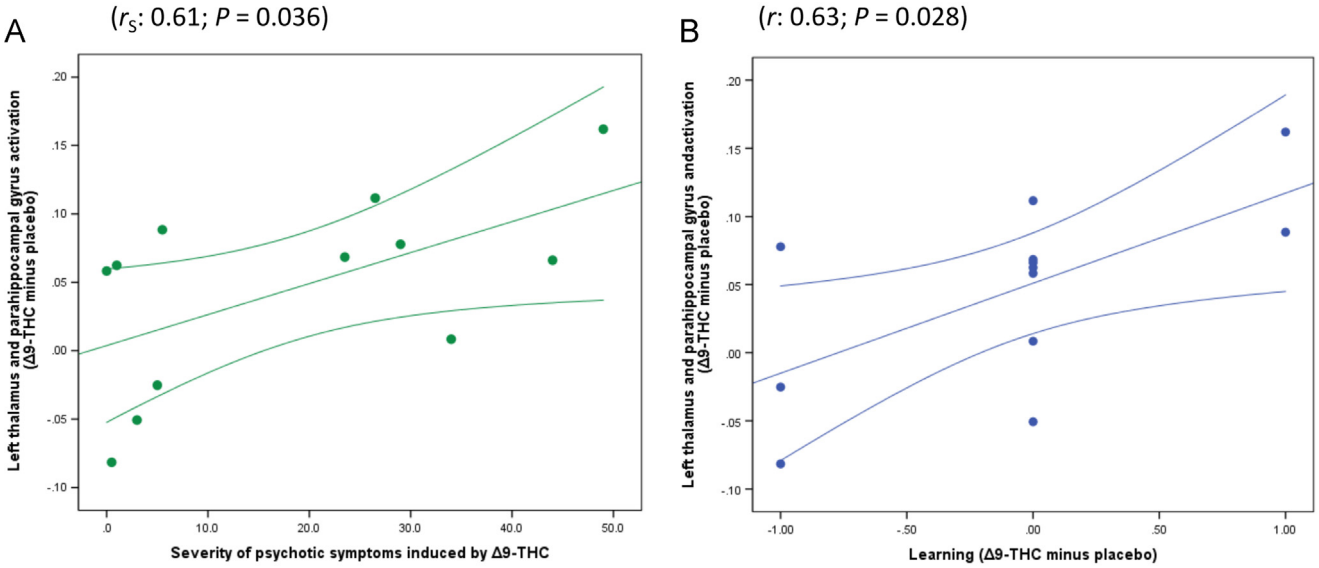

Fig. 3 Association between psychopathology, verbal learning, and left parahippocampal gyrus and thalamus activation after Δ9-THC administration in Non-users. Δ9-THC, (−)-trans-Δ9-tetrahydrocannabinol.

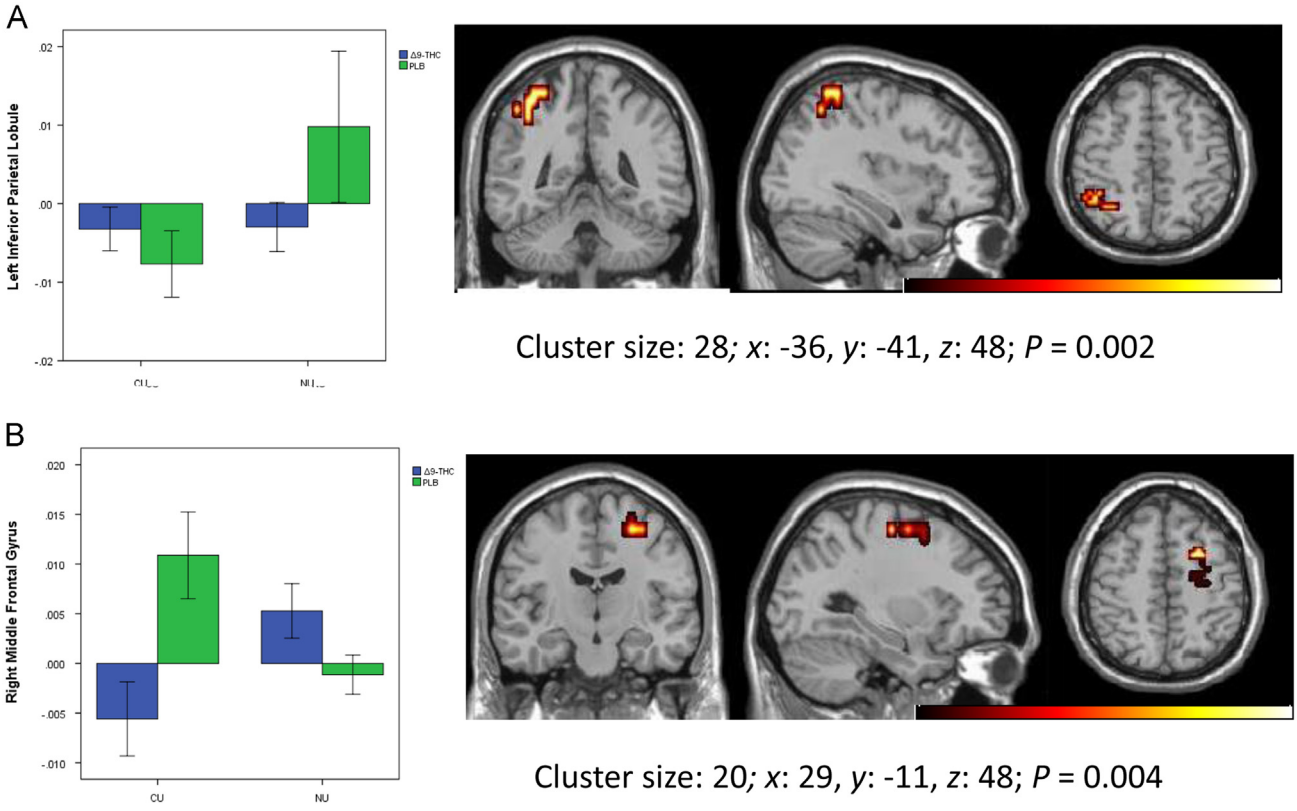

Fig. 4 Interaction between Δ9-THC administration and lifetime cannabis exposure on brain function during inhibition control processing. 'No-Go' condition ('No-Go' contrasted with 'Go') minus 'Oddball' condition ('Oddball' contrasted with 'Go'); Δ9-THC, (−)-trans-Δ9-tetrahydrocannabinol; PLB, Placebo; CU, Cannabis users; NU, Non-users; Y-axis displays SSQ statistic.

more than NU (Fig. S6A). CU also showed a lower activation in the left middle and superior temporal gyri compared to NU (Fig. S6B). Moreover, there was a main effect of Δ9-THC on brain activation, with greater right anterior cingulate (Fig. S7A) and lesser left insula activation (Fig. S7B) under Δ9-THC compared to placebo. There was an interaction between Δ9-THC administration and lifetime cannabis exposure (Fig. 4) such that, while under the placebo condition inhibitory control processing was associated with an activation in the left inferior parietal lobule in NU

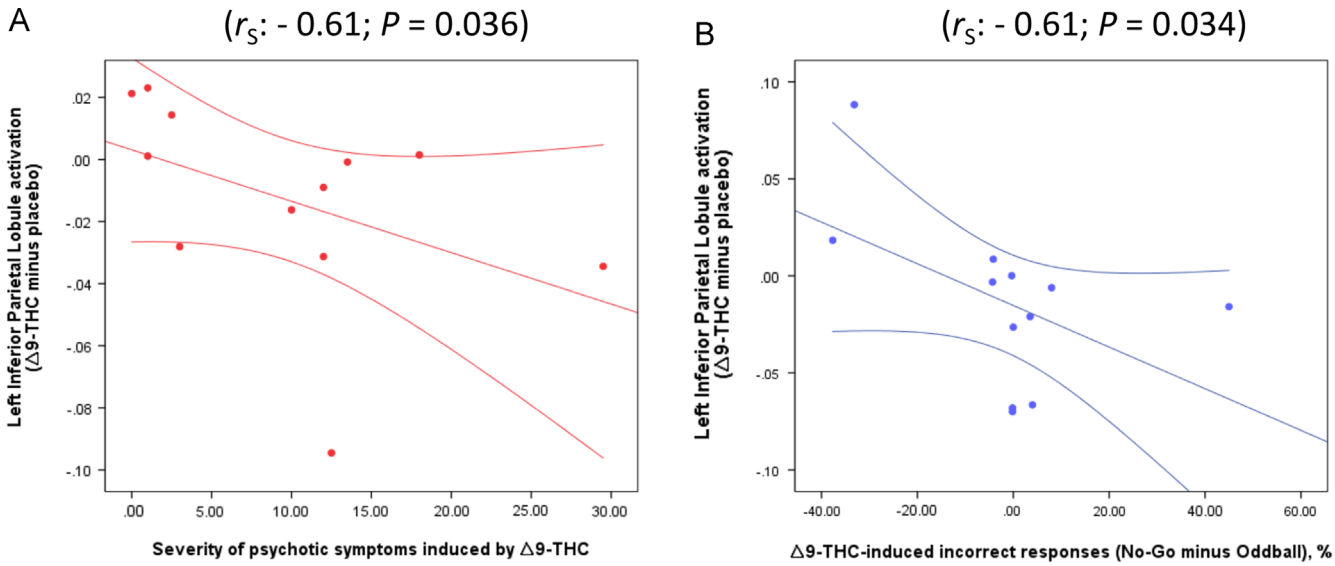

Fig. 5 Association between psychopathology, inhibitory control processing, and left inferior parietal lobule activation after Δ9-THC administration in Non-users. Δ9-THC, (−)-trans-Δ9-tetrahydrocannabinol.

individuals (control group), this brain area was deactivated in all the other groups (NU under the Δ9-THC condition; CU under the Δ9-THC and the placebo conditions; Fig. 4A). Moreover, while NU individuals under the placebo condition deactivated the right middle frontal gyrus, both NU under the Δ9-THC condition and CU under the placebo condition activated these areas. In contrast, CU under the Δ9-THC condition deactivated the right middle frontal gyrus, similarly to NU under placebo (Fig. 4B).

3.3.2.2. Association between psychopathological measures, behavioral performance, and brain activation during response inhibition. Due to the primary and selective involvement of left inferior parietal lobule during response inhibition control (Corbetta and Shulman, 2002; Kimberg et al., 2000; Sohn et al., 2000), and evidence from this study that the effect of Δ9-THC in this brain area differs between CU and NU, a correlation analysis was conducted to examine the relationship between patterns of brain activity in the left inferior parietal lobule and the behavioral measures which also appeared to differ in the two groups. Change in the left inferior parietal lobule activation induced by Δ9-THC (Δ9-THC minus placebo) negatively correlated with the severity of psychotic symptoms (rS: -0.61; P = 0.036; Fig. 5A) and the frequency of inhibition errors (Δ9-THC minus placebo; rS: -0.61; P = 0.034; Fig. 5B) induced by Δ9-THC in NU. Such correlations were not present in CU. Further, post-hoc testing indicated that the relationship between the effect of Δ9-THC on left inferior parietal lobule engagement was specific to psychotic-like symptoms under its influence, as such a relationship did not exist between the attenuation of left inferior parietal lobule engagement by Δ9-THC and its effect on the severity of intoxication, sedation, and anxiety symptoms.

4. Discussion

To our knowledge, this is the first report of the effects of previous cannabis exposure on the acute effects of Δ9-THC on the fMRI BOLD signal acquired during cognitive processing in man. Overall, results suggest that modest previous cannabis exposure is associated with disrupted brain activity and related cognitive impairments, but less pronounced responses to the psychotomimetic and neurocognitive effects of acute Δ9-THC administration.

Independent of the acute effects of Δ9-THC, CU displayed slower learning and greater engagement of the right caudate and parahippocampal gyrus (rPHG) than NU, suggesting that there were residual behavioural and neurophysiological effects of previous cannabis exposure. Similarly, compared to NU, during the response inhibition task (independent of Δ9-THC), CU made more inhibition errors and showed greater activation in the right inferior parietal lobule (rtIPL), superior temporal (rtSTG) and postcentral gyrus, and lower activation in the left middle and superior temporal gyri (ltMTG, ltSTG). Greater activation in task-related brain areas may represent a neurophysiological attempt to maintain compromised cognitive processing. Overall, these findings complement the existing larger body of research suggesting an association between cannabis use and verbal memory (Grant et al., 2003) as well as inhibitory control (Ganzer et al., 2016), and are in line with the evidence that deficits in memory, attention, and inhibition associated with cannabis use may persist after an adequate period of abstinence (Meier et al., 2012; Ganzer et al., 2016). Also, results from this study extend previous preclinical evidence (Kolb et al., 2006) as well as human studies (Gilman et al., 2014) suggesting that neurophysiological alterations can occur even after modest cannabis exposure.

The main aim of this study was to test the hypothesis that previous modest cannabis exposure modulated the behavioral and neurophysiological responses to acute administration of Δ9-THC. Compared to NU, abstinent CU showed a blunted response to the psychotomimetic effects of acute Δ9-THC administration, consistent with previous research indicating a less marked effect of Δ9-THC in frequent cannabis users relative to healthy controls (D'Souza et al., 2008b). Our neuroimaging findings extend these behavioral

findings (D'Souza et al., 2008b) and complement previous electrophysiological evidence (Cortes-Briones et al., 2015; D'Souza et al., 2012) by indicating that the blunted behavioral response observed in CU under the effects of Δ9-THC is also associated with a less marked neurophysiological disruption. In particular, under the influence of Δ9-THC, the pattern of brain activity observed in CU was similar to that adopted by NU under placebo. In healthy subjects, the rSTG, rIPL, and right precuneus are activated during the verbal learning task, reflecting the engagement of semantic and syntactic processing, deductive reasoning, and attentive control (Binder and Desai, 2011; Buchsbaum et al., 2011; Ciaramelli et al., 2008; Gaillard et al., 2011; Staresina and Davachi, 2006). However, NU in the presence of Δ9-THC and CU in the presence of placebo deactivated these areas, instead engaging the posterior cingulate gyrus and PHG, especially on the left side, consistent with previous evidence (Nestor et al., 2008). Hypoactivity in the temporal cortex and hyperactivity in the parahippocampus have been previously reported as a shift in brain activity identifying functional deficits and compensatory processes in CU (Nestor et al., 2008). Intriguingly, following Δ9-THC administration, CU activated rtIPL and right precuneus and only mildly engaged the ltPHG, partially reversing the deficits shown under placebo. During the response inhibition task, in order to perform the task NU under placebo activated the lIPL, a brain area selectively active at the time of a switch in discrimination tasks, reflecting the attentional adjustment needed to detect behaviorally relevant stimuli and elicit specific responses for a given task (Corbetta and Shulman, 2002; Kimberg et al., 2000; Sohn et al., 2000). Under acute (Δ9-THC challenge in NU) as well as residual (CU under placebo) effect of Δ9-THC, this brain area was deactivated in both groups, perhaps reflecting poorer performance in NU under Δ9-THC and CU under placebo who instead activated the right middle frontal gyrus (rtMFG). These findings may reflect an acute and long-term deleterious effect of cannabis on the ability to detect salient and unexpected stimuli requiring behavior modification such as response inhibition. Instead, CU under Δ9-THC did not engage the rtMFG, partially reversing the deactivation in the ltIPL shown under placebo. In NU, the severity of psychotic symptoms and cognitive impairments following acute Δ9-THC administration was more pronounced than in CU, and was associated with a more marked disruption of the underlying brain activity. This pattern was absent in CU, who under the acute Δ9-THC condition showed a less prominent alteration in verbal learning and inhibitory control-related brain activity.

To account for these findings, several explanations can be advanced, which are not mutually exclusive. Preclinical evidence suggests that prolonged exposure to Δ9-THC leads to the development of tolerance for most of its pharmacological effects by a reduction in the number and signaling efficiency of cannabinoid receptors type 1 (CB1R) as a homeostatic response (Gonzalez et al., 2005). Therefore, the present findings seem to suggest that the development of tolerance to the effects of Δ9-THC could occur even after modest cannabis exposure and persist after an adequate period of abstinence (3 months). In contrast, other human evidence indicates a rapid reversal of CB1R downregulation following abstinence in chronic (Hirvonen et al., 2012) and dependent users (D'Souza et al., 2016). However, CB1R downregulation following protracted cannabis use is not homogeneous across the brain. Chronic cannabis use is not associated with CB1R downregulation in the basal ganglia, midbrain and cerebellum, whilst inducing a downregulation of CB1R in the hippocampus, which doesn't reverse after abstinence (Hirvonen et al., 2012). Prolonged hippocampal CB1 downregulation could explain the persistence of tolerance to the effects of Δ9-THC after abstinence and has also been proposed to contribute to the residual cognitive impairments associated with cannabis use (D'Souza, 2007). Future studies should therefore determine whether differing patterns of CB1R downregulation in different brain regions may underlie differing susceptibility to development of tolerance of the different behavioural and neurocognitive effects of cannabis.

It is also possible that underlying systematic differences in endocannabinoid signaling between the CU and NU groups linked to their distinct previous cannabis exposure history (Colizzi et al., 2015c; Taurisano et al., 2016) may have played a role in determining the precise direction of the pharmacological effect of Δ9-THC at the CB1 receptors, where it is known to have a partial agonist effect, thereby influencing systems-level effects indexed using fMRI. Preclinical evidence (Bilkei-Gorzo et al., 2017) is consistent with such a possibility and evidence that the effects of Δ9-THC are influenced by CB1R expression level and signalling efficiency as well as ongoing endocannabinoid tone (Pertwee, 2008). Alternatively, we cannot exclude that CU under acute intoxication are no longer able to engage/ shift to additional brain areas as a compensatory strategy, suggesting a more pronounced cognitive dysfunction upon heavier cannabis use and/or while performing more demanding cognitive tasks. Preclinical evidence suggests that long-term exposure to Δ9-THC can alter the modulatory effect of endogenous and exogenous cannabinoids on synaptic transmission in brain areas relevant to cognitive processing (Colizzi et al., 2016b). However, the present study was not designed to examine these possibilities, which should be investigated in future studies.

The main strengths of the present study are the use of a control group of NU, an adequate period of abstinence, especially among CU confirmed with negative urine drug screen, and the fMRI design which allowed investigation of the neurophysiological underpinnings of cognitive impairments observed following both acute and non-acute cannabis exposure. On the other hand, as the CU individuals in this study were not heavy cannabis users, these results may not reflect what happens following abstinence in those with heavier patterns of use. Also, cumulative lifetime cannabis exposure was not measured using specific exposure constructs which could have offered a more reliable retrospective measure (Rabin et al., 2013). Moreover, as cannabis and tobacco are commonly smoked together, possible synergistic effects of the two substances deserve further investigation. However, given the modest cannabis use as well as the absence of heavy tobacco smokers in the study sample, this is unlikely to have systematically affected the results. As we studied only male participants in order to have a more homogenous sample, this limits generalizability to female cannabis users, which should be addressed in future investigations. The small sample size and the use of a

1.5 T MR scanner and a relatively large voxel size represent limitations to be considered.

Further investigation of the neurochemical explanations for the present findings and implications for mechanisms underlying the association between cannabis use and psychosis is warranted.

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Contributors

All authors designed the study and wrote the protocol. Author MC and SB managed the literature searches and statistical as well as imaging analyses. Authors MC and SB wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.euroneuro.2018.04.003.

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