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Disrupted Gamma-Band Neural Oscillations During Coherent Motion Perception in Heavy Cannabis Users

Patrick D Skosnik*[1], Giri P Krishnan[2], Deepak C D'Souza[1], William P Hetrick[3] and Brian F O'Donnell[3]

[1]Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA; [2]Department of Cell Biology and Neuroscience, University of California, Riverside, Riverside, CA, USA; [3]Department of Psychological and Brain Sciences, Indiana University, Bloomington, IN, USA

Previous work in animals and humans has shown that exogenous cannabinoids disrupt time-locked, evoked gamma oscillations (30–80 Hz). However, no studies to date have examined the effect of cannabis on non-time-locked, induced gamma oscillations during more complex Gestalt perception. The current study therefore utilized electroencephalography (EEG) to examine gamma oscillations during coherent motion perception in heavy cannabis users and controls. Chronic cannabis users ($n = 24$; 12 h abstinence before study; positive 11-*nor*-9-carboxy-delta-9-tetrahydrocannabinol urine levels) and cannabis-naive controls ($n = 23$) were evaluated. Stimuli consisted of random dot kinetograms (RDKs) that subjects passively viewed during three different conditions: coherent motion, incoherent motion, and static. Time × frequency analysis on EEG data was performed using Fourier-based mean trial power (MTP). Transient event-related potentials (ERPs) to stimulus onset (visual N100 and P200 components) were also evaluated. The results showed that the coherent motion condition produced a robust increase in neural activity in the gamma range (induced power from 40 to 59 Hz) as compared with the incoherent motion and static conditions. As predicted, the cannabis group showed significant reductions in induced gamma power in the coherent condition relative to healthy controls. No differences were observed between the groups in the N100 or P200 components, indicating intact primary sensory processing. Finally, cannabis users showed a trend toward increased scores on the Chapman Perceptual Aberration Scale (PAS) that was positively correlated with total years of active cannabis use. These data suggest that cannabis use may interfere with the generation of induced gamma-band neural oscillations that could in part mediate the perceptual-altering effects of exogenous cannabinoids.

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INTRODUCTION

Although cannabis has consistently been the most commonly used illicit drug in the United States (SAMHSA, 2012), the deleterious consequences of its use have only recently been recognized. For example, there is now convincing evidence that persistent cannabis use, particularly during adolescence, is associated with lasting impairments in perceptual and cognitive function (Meier *et al*, 2012; Semple *et al*, 2003; Skosnik *et al*, 2012; Solowij *et al*, 2002). Furthermore, heavy use of cannabis is now known to be a risk factor for the development of psychiatric disorders, most notably schizophrenia (Large *et al*, 2011; Moore *et al*, 2007). Most importantly, with the legalization of medicinal cannabis (Kleber and DuPont, 2012; Procon.org., 2011), the decriminalization of cannabis in some states in the United States (Bly, 2012), the high rates (ONDCP OoNDCP, 2008) and earlier age of onset of cannabis use (Johnston *et al*,

2012), the increasing potency of cannabis (Mehmedic *et al*, 2010), and the recreational use of highly potent synthetic cannabinoids (eg, Spice and K-2) (Johnson *et al*, 2011; Vardakou *et al*, 2010), there is an urgent need to understand the neural mechanisms underlying the perceptual and cognitive effects of exogenous cannabinoids.

Cannabis, and its primary psychoactive constituent Δ^9-tetrahydrocannabinol (THC) (Gaoni and Mechoulam, 1971), affects the brain through the activation of central cannabinoid-1 receptors (CB1Rs) (Devane *et al*, 1988; Pertwee *et al*, 2010). CB1Rs, which are the most highly expressed metabotropic receptors in the mammalian brain, are primarily localized to the cerebral cortex, basal ganglia, hippocampus, and cerebellum (Egertova and Elphick, 2000; Eggan and Lewis, 2007; Glass *et al*, 1997; Herkenham *et al*, 1990; Pertwee, 1997, 1999; Tsou *et al*, 1998). In the cerebral cortex and hippocampus, presynaptic CB1Rs inhibit the release of γ-aminobutyric acid (GABA) from cholecystokinin (CCK)-containing interneurons (Ali and Todorova, 2010; Bacci *et al*, 2004; Bodor *et al*, 2005; Eggan and Lewis, 2007; Eggan *et al*, 2010; Foldy *et al*, 2006; Hill *et al*, 2007; Katona *et al*, 2000). One of the primary functions of interneuron networks is the generation and maintenance of gamma-range (30–80 Hz) neural oscillations (Buzsaki and Wang, 2012; Gonzalez-Burgos and Lewis, 2008; Traub *et al*,

*Correspondence: Dr PD Skosnik, Department of Psychiatry, Yale University, Yale University School of Medicine, 300 George Street, New Haven, CT 06510, USA, Tel: +1 812 320 2521, Fax: +1 203 937 4860, E-mail: patrick.skosnik@yale.edu

1996, 2003; Uhlhaas and Singer, 2010; Whittington *et al*, 1995) that are thought to play a key role in sensory registration, the integration and binding of perceptual features, associative learning, and conscious awareness (Melloni *et al*, 2007; Singer, 1999; Uhlhaas *et al*, 2009; Wang, 2010; Whittington *et al*, 2000). Consequently, it has been suggested that exogenous cannabinoids may interfere with normal perception and cognition via the desynchronization of neural oscillations in the gamma range (Skosnik *et al*, 2006a).

In support of this postulate, *in vitro* slice studies have demonstrated that the application of both CB1R agonists (Hajos *et al*, 2000) and inverse agonists (Morgan *et al*, 2008) can disrupt the ability of neural networks to oscillate at gamma frequencies. Several *in vivo* animal studies utilizing local field potentials (LFPs) have also shown that exogenous cannabinoids can disrupt gamma rhythms (Hajos *et al*, 2008; Robbe *et al*, 2006). For example, Hajos *et al* (2008) observed that rats engaged in an auditory sensory gating paradigm exhibited decreases in gamma (and theta) power to click stimuli after the administration of the CB1R agonist CP-55940. These findings were CB1R specific, as the alterations in gamma oscillations were reversed by the CB1R antagonist AM-251. Most recently, Sales-Carbonell *et al* (2013) utilized neocortical electrocorticograms in mice and found that systemic administration of CP-55940 decreased the amplitude of neural oscillations >12 Hz (ie, beta and gamma bands). Just as in the study of Hajos *et al* (2008), this decrease was blocked by the coadministration of AM-251 (Sales-Carbonell *et al*, 2013).

Regarding humans studies, several experiments have demonstrated that chronic cannabis users show evidence of altered gamma rhythms utilizing both evoked and steady-state electroencephalography (EEG) (Edwards *et al*, 2009; Skosnik *et al*, , 2006a, 2012). EEG is ideal for the study of neural oscillations, as the signals detected represent actual neural events (summed postsynaptic field potentials), and are recorded with millisecond-range temporal resolution (Luck *et al*, 2011). The types of neural oscillations in human EEG studies are typically classified as evoked, steady state, or induced (Bertrand and Tallon-Baudry, 2000; Galambos, 1992). Transient, time-locked EEG responses typically occur a few hundred milliseconds after the presentation of discrete sensory stimuli (tones or clicks), are phase-locked to stimulus onset, and are termed *evoked* oscillations (Pantev *et al*, 1991; Roach and Mathalon, 2008). Periodic/rhythmic stimuli (clicks or flashes) presented at specific frequencies can be used to entrain the EEG to a particular phase and frequency, and are utilized to test the capacity of neural networks to oscillate at functionally relevant frequencies (eg, gamma). These are often referred to as auditory or visual *steady-state responses* (Galambos *et al*, 1981; Kwon *et al*, 1999; Picton *et al*, 2003; Spencer *et al*, 2008). Finally, gamma oscillations can occur at variable phases or latencies with respect to stimulus onset, particularly during perceptual and cognitive tasks. These latency-varying responses are collectively referred to as *induced* oscillations. Induced gamma rhythms typically occur later than evoked oscillations (~200–500 ms after stimulus onset), and are cancelled out after standard EEG trial averaging (as is used in the processing of evoked and steady-state responses) (Herrmann and Knight, 2001; Krishnan *et al*, 2005; Roach and Mathalon, 2008).

Using an auditory sensory gating paradigm similar to that utilized by Hajos *et al* (2008), Edwards *et al* (2009) demonstrated significant reductions in *evoked* gamma power and phase locking to click stimuli in chronic cannabis users (Edwards *et al*, 2009). Similarly, Skosnik *et al* (2006a; 2012) observed decreases in *steady-state* 40 Hz spectral power during an auditory entrainment paradigm that correlated with age of onset of cannabis use (Skosnik *et al*, 2012). These data thus provided the first evidence in humans that exogenous cannabinoids can disrupt evoked and steady-state gamma rhythms. However, no studies to date have examined whether cannabinoids can affect *induced* oscillations, particularly in the context of more complex perceptual processing.

As alluded to above, induced gamma oscillations may represent a neural correlate for various higher perceptual and cognitive processes including learning and memory, visual object representation, and perceptual binding (Bertrand and Tallon-Baudry, 2000; Buzsaki and Draguhn, 2004; Kaiser and Lutzenberger, 2003; Singer, 1999; Tallon-Baudry, 2009). Hence, whereas early evoked gamma rhythms are likely involved in sensory registration and the encoding of basic stimulus features, induced gamma oscillations may play a key role in the synchronization or 'binding' of neural assemblies involved in the generation of coherent cortical representations (ie, Gestalt perception). One domain where induced gamma has been shown to be especially relevant is visual motion perception. Motion perception, particularly coherent motion perception, requires the integration of local motion signals from various parts of the visual field into a global percept of two-dimensional motion (that likely occurs in area V5/MT) (Andersen, 1997; Born and Bradley, 2005; Heeger *et al*, 1999; Khayat *et al*, 2010; Muckli *et al*, 2002; Snowden *et al*, 1991). This integration of local motion signals from striate and prestriate visual cortices could be accomplished by gamma-range synchronization of neural populations within area MT. Indeed, numerous animal and human studies have shown that gamma power increases during the perception of coherent motion (Gray *et al*, 1990; Khayat *et al*, 2010; Krishnan *et al*, 2005; Kruse and Eckhorn, 1996; Lutzenberger *et al*, 1995; Muller *et al*, 1997; Naue *et al*, 2011; Schanze and Eckhorn, 1997; Siegel *et al*, 2007; Swettenham *et al*, 2009). For example, in a human EEG study, Krishnan *et al* (2005) utilized random dot kinetograms (RDKs) to demonstrate that coherent motion increased induced gamma power compared with incoherent or static stimuli. Similar results were observed in a human magnetoencephalography (MEG) study (Siegel *et al*, 2007), wherein gamma-band activity to coherent stimuli peaked in the lateral occipitotemporal cortex (an area corresponding to the visual motion area MT). Interestingly, in primate brain, area MT contains nearly twice the number of CB1Rs as compared with primary visual cortex (Eggan and Lewis, 2007). This, along with the role of CB1Rs in modulating GABA-mediated network oscillations discussed above, provides the impetus for studying the effect of chronic cannabinoids on gamma rhythms during motion perception.

The current study therefore examined the effect of chronic cannabis use on induced gamma oscillations utilizing a well-validated coherent motion perception paradigm (Brecht *et al*, 2001; Krishnan *et al*, 2005; Kruse and Hoffmann, 2002; Siegel *et al*, 2007). Based on previous animal and human work, it was hypothesized that the cannabis group would

exhibit decreased induced gamma power during the perception of coherent motion. It was further predicted that cannabis users would exhibit intact visual event-related potentials (N100 and P200) to stimulus onset, indicating intact primary visual processing.

MATERIALS AND METHODS

Subjects

Current cannabis users ($n = 24$) and healthy drug-naive controls ($n = 23$) were recruited from the local university community, paid for their participation, and written informed consent was obtained from each. Table 1 illustrates basic demographic information as well as drug/alcohol use rates. There were no significant differences between the groups in age, years of education, or WAIS scores (Table 1).

The inclusion criteria were as follows: (1) For the cannabis group: current cannabis consumption (smoked joints) at the rate of at least once per week during the past month, a positive urine toxicology screen for THC metabolites (11-*nor*-Δ-9-THC-9-carboxylic acid), no other illicit substance use during the past 3 months (including a negative urine toxicology screen for other illicit drugs), and no DSM-IV diagnosis of Axis I or II disorders except cannabis abuse or dependence; (2) For the control group: no history of illicit substance use, a negative urine toxicology screen for all drugs tested, and no history of psychiatric illness (Axis I or II); (3) For all participants: ages 18–35 years, completion of high school education, no family history of schizophrenia or bipolar disorder, no history of cardiovascular disease, hearing problems, neurological disease, learning disability, or head injury resulting in loss of consciousness. In addition, participants were excluded if they reported consumption of more than 2 alcoholic drinks per day (1 per day for females). The cannabis group drug-use inclusion criteria (minimum cannabis use at least once per week; 24 h abstinence) was chosen to minimize acute cannabis effects, while retaining possible neurophysiological effects from altered CB1 activity. Human studies indicate that 80–90% of the total amount of THC is excreted within 5 days, and hence a minimum use of once per week enabled detection of THC metabolites (Hunt and Jones, 1980). Furthermore, previous work has shown that cannabis exposure of as little as once per week is enough to disrupt the behavioral and neuroendocrine response to THC (D'Souza et al, 2008). However, it should be noted that this requirement was simply a minimum for inclusion into the cannabis group, and the mean level of use was much higher (mean joints per week = 11.4; SD = 8.5; see Table 1).

Clinical Interviews, Questionnaires, and Drug-Use Assessment

The Structured Clinical Interview for DSM-IV Axis I and II Disorders (SCID I and SCID II) were administered to assess current and past history of psychopathology. The SCID I module E and a locally developed drug-use questionnaire based on a timeline followback approach were used to ascertain current and past diagnoses for alcohol and substance abuse and dependence. Levels of cannabis consumption (estimated number of joints) were determined via the interview and questionnaire for lifetime, the past six 6, 3 months, 1 month, and then for the week before the test session as has been described previously (Fridberg et al, 2011; Skosnik et al, 2006a, 2008, 2012). Participants were instructed to consider each day of the week and indicate, for an average week, how much they consumed per drug-use occasion for each length of time assessed. Age of first use, average number of joints smoked per week during the past month, and time since last use are reported in Table 1.

Urine drug screens (Q10-1, Proxam) were administered immediately preceding EEG testing in order to corroborate self-reports from the drug questionnaire and clinical

Table 1 Subject Demographics, WAIS and PAS Scores, and Substance Use Characteristics (Mean (SD))

	Cannabis users ($n = 24$)	Controls ($n = 23$)	*P*-value
Age (years)	21.4 (2.7)	21.6 (3.0)	$p = 0.46$
Education (years)	14.5 (1.5)	15.0 (1.7)	$p = 0.14$
Gender (no. of females)[a]	9	12	$p = 0.31$
WAIS (piccom) scores	12.0 (0.5)	12.7 (0.6)	$p = 0.34$
WAIS (digit) scores	10.7 (0.4)	11.7 (0.6)	$p = 0.15$
WAIS (sim) scores	12.6 (0.4)	12.3 (0.5)	$p = 0.56$
WAIS (dspan) scores	11.9 (0.5)	10.7 (0.5)	$p = 0.12$
Perceptual aberration scale (PAS) scores	3.2 (6.1)	1.2 (1.9)	$p = 0.1$
Average number of alcoholic drinks/week (past month)	4.6 (4.1)	0.9 (2.5)	$p < \textbf{0.001}$
Average number of cigarettes/week (past month)	3.4 (5.9)	1.1 (4.2)	$p = 0.12$
Age of first cannabis use	15.4 (1.5)	—	—
Total years of cannabis use	5.6 (3.0)	—	—
Average number of joints/week (past month)	11.4 (8.5)	—	—
Hours since last cannabis use (hours)	42.9 (29.7)	—	—

[a]Results of χ^2 test.
Note that WAIS version was the WAIS-III. Subscales included were picture completion (piccom), digit symbol (digit), similarities (sim), and digit span (dspan).
Bold value indicates statistical significance.

interviews. The Q10-1 kit screens for cannabis (THC-COOH; 50 ng/ml sensitivity), opiates, amphetamines, cocaine, MDMA (ecstasy), tricyclic antidepressants, phencyclidine, benzodiazepines, methamphetamines, and barbiturates.

In addition to assessment of psychopathology and substance use, subscales of the Wechsler Adult Intelligence Scale III (WAIS-III; Picture completion, Digit Symbol, Similarities, and Digit Span) were used to assess possible deficits in general neuropsychological function. The Chapman Perceptual Aberration Scale (PAS) was also administered in order to assess general disturbances in subjective perceptual experience (Chapman et al, 1978).

RDK Moving Dot Procedure

The moving dot paradigm was the same as that described previously (Krishnan et al, 2005). Briefly, subjects were asked to relax, keep their eyes open, and focus on the display during stimulus presentation. All stimuli were presented in a Power Macintosh computer (5.9×6.6 degrees of visual angle; 80 cd/m^2). The experiment included three conditions: coherent motion, incoherent motion, and a static dot display. In the coherent condition, all dots in the RDK were displaced from left to right within the stimulus window. In the incoherent condition, all dots were displaced at randomly generated angles, whereas the dots were stationary in the static condition. A total of 100 dots were used to generate the RDK in each condition. The stimulus window subtended five degrees of the visual angle and the rate of displacement of dots was five degrees per second. The position of dots was refreshed every 107.5 ms (9.3 Hz) for both the coherent and incoherent conditions. All trials were presented for 1500 ms, with a 1.5-s interval between trials. There were 100 trials in each condition. The conditions were randomized across trials and subjects were given brief breaks after every 50 trials.

EEG Recording and Signal Analysis

EEG recording and preprocessing. The EEG was recorded continuously (band pass 0.1–100 Hz; sampling rate 1000 Hz) from the scalp using a 32 channel electrode cap with a nose reference, along with additional electrodes to record the vertical electrooculogram (VEOG; Neuroscan SynAmps, Compumedics Neuroscan, Charlotte, NC). Electrode impedances were maintained below 10 kΩ. The recorded EEG was segmented into epochs consisting of 1500 ms during stimulus presentation, along with 500 ms baseline and 500 ms offset period. Any trial with a voltage greater than ± 100 µV was excluded from analysis. All subjects had at least 75% trials retained after artifact rejection. Ocular movement correction was applied using Gratton's algorithm (Gratton et al, 1983). All initial EEG processing was performed using commercially available software (Analyzer 2.0, Brain Products GmbH, Germany).

EEG signal analysis. Induced gamma activity was measured as mean trial power (MTP) using a time × frequency spectrogram with the Signal Processing and EEGLab toolbox in MATLAB (Delorme and Makeig, 2004; Rass et al, 2010; Skosnik et al, 2006b, 2012). For MTP, a baseline normalized event-related spectral perturbation (ERSP) was

obtained by applying a Fast Fourier Transform (FFT) using a time-sliding window on single trial data. This results in a time × frequency transform consisting of a complex number for every time point, frequency, and trial. The 500 ms interval before stimulus onset was used as the baseline for computing the ERSP, and the sliding window had a duration of 128 ms. After sufficient padding a frequency resolution of 0.98 Hz was obtained and the time resolution was 3.8 ms. A Hanning window (100%) was applied on the data before the FFT. No other taper functions were used. Thus, MTP represents the average of spectral power from individual trials after subtracting the mean from the baseline period (500 ms before stimulus onset). Power values in the gamma-band range (frequency bins from 40 to 59 Hz) were averaged using sequential 100 ms windows between onset and offset of the stimuli (1500 ms) for every subject and channel as reported previously (Krishnan et al, 2005). For statistical analysis, a single value was calculated for MTP from 40 to 59 Hz for the entire interval during stimulation (average MTP between 0 and 1500 ms). Data from Fz, Cz, Pz, and Oz were used for analysis of induced gamma. Finally, in order to rule out that baseline/resting gamma power affected the induced gamma results, an FFT was used to calculate single trial spectral power (40–59 Hz) during the stimulus-free baseline period (− 500 to 0 ms).

For analysis of the transient visual evoked responses (N100 and P200), epochs were low-pass filtered at 15 Hz (24 dB/octave) before averaging, and were baseline corrected (500 ms prestimulus baseline) after averaging. Peak amplitude and latency values after stimulus onset were used as the dependent measures, and were obtained for each electrode within the time window of interest using an automated algorithm (Analyzer 2.0, Brain Products GmbH). N100 was defined as the most negative voltage between 80 and 220 ms after stimulus onset and P200 was defined as the most positive voltage between 180 and 320 ms after stimulus onset. Data from the midline electrode sites Fz, Cz, Pz, and Oz were used for analysis of the N100 and P200.

Statistical Analysis

For induced gamma activity (MTP), the primary comparisons of interest were the coherent vs incoherent conditions and the coherent vs static conditions. A repeated measures ANOVA was utilized to determine the between subjects factor of group (2), and the within-subjects factor of condition (2; coherent vs incoherent and coherent vs static) and electrode (4). For the transient N100 and P200 ERPs, amplitude and latency were assessed using repeated measures ANOVA that examined the between-subjects factor of group (2), and the within-subjects factors of condition (2; coherent vs incoherent and coherent vs static) and electrode (4). In order to examine baseline/resting gamma power, repeated measures ANOVA was used to assess the effect of group (2) and electrode (4). Greenhouse–Geisser corrections for nonsphericity were used where appropriate. The addition of gender, age, and level of alcohol or tobacco use as covariates did not alter the results of the induced gamma or ERP analyses. All EEG data were normally distributed, as assessed with Shapiro–Wilk tests for normality. In order to examine possible relationships between variables, Pearson's correlation coefficients were utilized. A criterion of $p < 0.05$

was used throughout to determine statistical significance, and all tests were two tailed. All analyses were conducted in the software package PASW Statistics 18.0.

RESULTS

Demographics, WAIS and PAS Scores, and Substance Use Data

Table 1 provides basic demographic information, WAIS, PAS, and substance use data. A one-way ANOVA revealed that there were no significant differences between the groups in age, years of education, or WAIS-III subscale scores. The χ^2 test showed that the gender proportion within each group was not significantly different (Table 1). Because of the stringent exclusion criteria (see above), alcohol and tobacco use rates for both groups were extremely low, and not clinically relevant. However, there was a significant difference in the average number of alcoholic drinks consumed per week between the two groups (Table 1). Furthermore, 62.5% of the sample of cannabis users met criteria for cannabis abuse or dependence. However, none of the subjects met DSM-IV criteria for alcohol or other substance abuse or dependence. Finally, a one-way ANOVA revealed a trend toward increased PAS scores in the cannabis group compared with healthy controls (F(1, 45) = 2.39, $p = 0.1$; Table 1).

Induced Gamma Activity

Figures 1–3 illustrate induced gamma power between the groups for all three conditions from the four midline electrode sites. Figure 4 shows average MTP during the period of stimulation (0–1.5 s) for the groups in each of the conditions at electrode Cz. For the comparison between the *coherent* and *incoherent* motion conditions, the repeated measures ANOVA revealed a main effect of condition (F(1, 45) = 45.22, $p < 0.001$) indicating greater gamma power in the coherent motion condition (Figures 1 and 2). Furthermore, a significant group × condition interaction was observed (F(1, 45) = 6.27, $p < 0.016$), indicating differential induced gamma activity in the coherent *vs* incoherent motion conditions between the cannabis and control groups (Figure 4a and b). The *post hoc* ANOVAs comparing the groups in the coherent and incoherent conditions separately indicated that the cannabis group had decreased gamma power compared with controls in the coherent condition (F(4, 42) = 5.16, $p < 0.002$). There was no significant difference between the groups in the incoherent condition (F(4, 42) = 0.99, $p = 0.42$). A significant electrode × condition was also observed (F(3, 135) = 5.3, $p < 0.002$).

For the comparison between the *coherent* motion and *static* conditions, the repeated measures ANOVA revealed a trend toward a condition × electrode interaction (F(3, 135) = 2.40, $p < 0.071$) and a trend toward a condition × electrode × group interaction (F(3, 135) = 2.35, $p < 0.075$; Figures 2, 3, and 4b and c). No other trends or significant effects were observed.

Finally, comparisons examining baseline/resting gamma power revealed a main effect of electrode (F(3, 135) = 23.0, $p < 0.001$). However, no main effect of group (F(1, 45) = 2.42, $p = 0.13$) or electrode × group interaction (F(3, 135) = 0.26, $p = 0.85$) was observed (data not shown).

Transient ERPs (N100 and P200)

For the comparison between the *coherent* and *incoherent* motion conditions for N100 amplitude, the repeated measures ANOVA revealed a main effect of electrode (F(3, 135) = 7.16, $p < 0.001$). No other main effects or interactions were observed. For N100 latency, the ANOVA revealed a main effect of electrode (F(3, 135) = 23.75, $p < 0.001$) and an electrode × condition interaction (F(3, 135) = 7.07, $p < 0.001$). No other significant effects were observed.

For P200 amplitude in the coherent *vs* incoherent conditions, a main effect of electrode was observed (F(3, 135) = 49.84, $p < 0.001$). No other main effects or interactions were observed. For P200 latency, the ANOVA revealed a main effect of electrode (F(3, 135) = 3.56, $p < 0.016$) and an electrode × condition interaction (F(, 45) = 4.64, $p < 0.004$). No other main effects or interactions were observed. For illustrative purposes, grand-averaged N100–P200 waveforms and topographic head maps for the cannabis and healthy control groups from the coherent motion condition are shown in Figure 5.

For the comparison between the *coherent* motion and *static* conditions for N100 amplitude, the repeated measures ANOVA revealed a main effect of electrode (F(3, 135) = 4.82, $p < 0.003$) and a group × condition interaction (F(1, 45) = 4.46, $p < 0.04$). However, *post hoc* ANOVAs examining N100 amplitude separately for the coherent (F(4, 42) = 0.48, $p = 0.75$) and static (F(4, 142) = 1.35, $p = 0.27$) conditions revealed no group differences. For N100 latency, only a main effect of electrode was observed (F(3, 135) = 15.33, $p < 0.001$). Finally, for P200 amplitude, the ANOVA revealed a main effect of condition (F(1, 45) = 15.27, $p < 0.001$) and electrode (F(3, 135) = 59.10, $p < 0.001$), and a condition × electrode interaction (F(3, 135) = 11.55, $p < 0.001$). For P200 latency, no significant effects were observed.

Correlations

Potential associations (chosen *a priori*) between cannabis use variables (age of first use, total years of use, and number of joints in the past month) and induced gamma power (power values during the coherent condition at electrode Cz (where power was maximal)) and PAS scores were examined. Whereas no associations were observed for induced gamma activity, a significant positive correlation was observed for total years of cannabis use and PAS scores ($r = 0.45$, $p < 0.026$; Figure 6a). However, visualization of the data and further analysis revealed that one of the subjects represented an outlier (see circled data point in Figure 6a). Therefore, the correlation coefficient was recalculated with the removal of this subject. As can be seen in Figure 6b, the positive correlation between total years of cannabis use and PAS scores survived despite the exclusion of the outlier ($r = 0.44$, $p < 0.033$).

DISCUSSION

The present study examined induced gamma oscillations during coherent motion perception via EEG in the context of chronic cannabinoids. As in previous work utilizing RDKs in humans (Krishnan *et al*, 2005; Siegel *et al*, 2007), the perception of coherent motion resulted in a robust
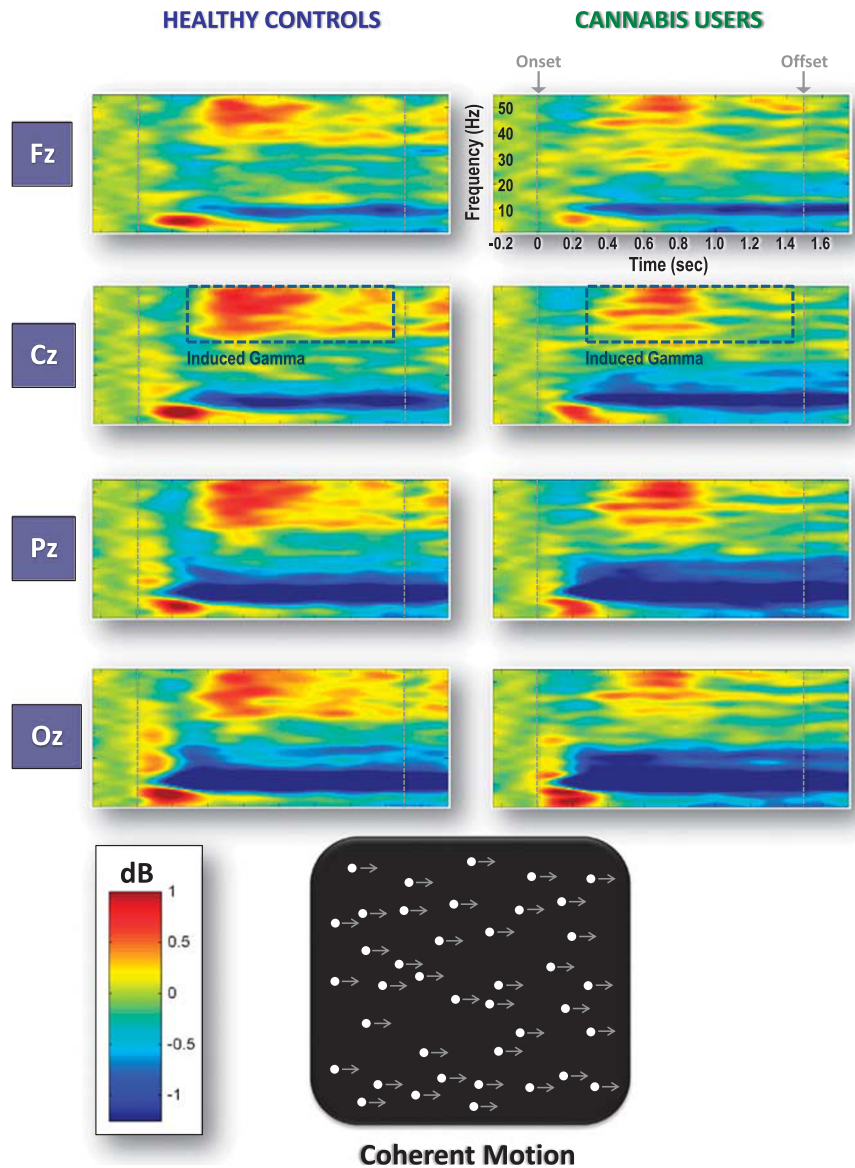
Figure 1 Grand-averaged time × frequency plots demonstrating mean trial power (MTP) for midline electrodes during the coherent motion condition for the healthy control and cannabis groups.

increase in induced gamma rhythms compared with incoherent motion or static stimuli (Figures 1–3). This replicates a host of animal and human studies demonstrating that gamma power is increased during the perception of coherent motion (Gray et al, 1990; Khayat et al, 2010; Krishnan et al, 2005; Kruse and Eckhorn, 1996; Lutzenberger et al, 1995; Muller et al, 1997; Naue et al, 2011; Schanze and Eckhorn, 1997; Siegel et al, 2007; Swettenham et al, 2009). Regarding the comparison of the control and cannabis groups, it was observed that cannabis users had significantly decreased induced gamma power in the coherent motion condition compared with healthy controls (Figures 1 and 4). This deficit was unlikely because of alterations in primary visual processing, as early ERPs (N100 and P200) to the RDK stimuli were not different between the control and cannabis groups (Figure 5). Finally, cannabis users exhibited greater self-reported perceptual anomalies (as indicated by

higher scores on the PAS) that were positively correlated with total years of cannabis use (Figure 6).

This is the first study of induced gamma rhythms in the context of chronic exogenous cannabinoids in humans. The current results extend previous human work on evoked and steady-state gamma oscillations in cannabis users (Edwards et al, 2009; Skosnik et al, 2006a, 2012). For example, Skosnik et al (2012) demonstrated 40 Hz gamma-range deficits in spectral power using the auditory state paradigm. As in the current study, no differences were observed in early auditory ERPs (N100), indicating intact primary sensory processing. It thus appears that chronic cannabinoids influence synchronized oscillations in higher cortical areas (association cortex), whereas they have less impact on primary sensory cortex. The fact that association areas exhibit higher levels of CB1Rs as compared with primary sensory cortex provides anatomical support for this
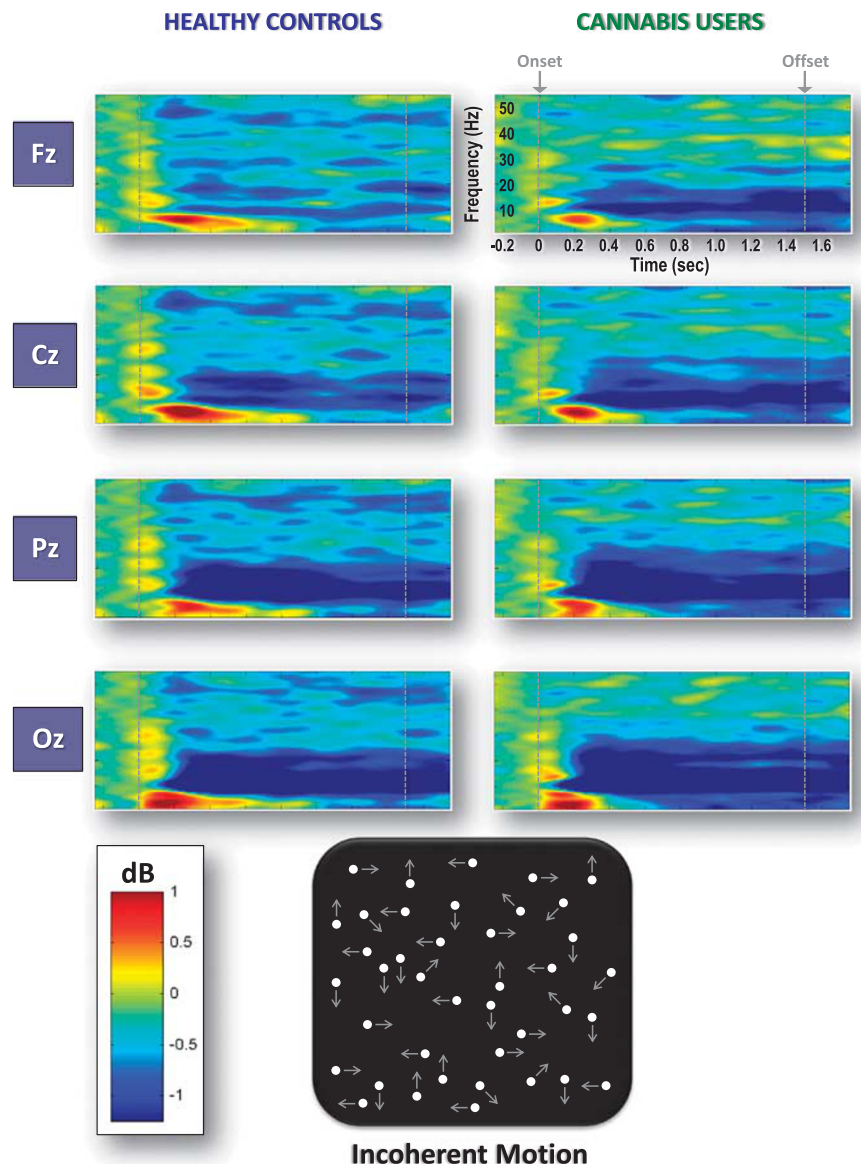
Figure 2 Grand-averaged time × frequency plots demonstrating mean trial power (MTP) for midline electrodes during the incoherent motion condition for the healthy control and cannabis groups.

interpretation (Eggan and Lewis, 2007). In addition, total years of cannabis use were related to self-reported perceptual anomalies. This suggests that in addition to alterations in induced gamma oscillations, chronic cannabinoids are associated with lasting changes in perceptual processing.

The results of human studies demonstrating abnormalities in gamma-band neural oscillations in chronic cannabis users are also consistent with a host of *in vitro* and *in vivo* studies of acute cannabinoid effects in animals (Hajos *et al*, 2000, 2008; Morgan *et al*, 2008; Robbe *et al*, 2006; Sales-Carbonell *et al*, 2013). These converging lines of evidence suggest that cannabinoids play a general role in the generation and maintenance of neural synchrony, particularly in the gamma range. Indeed, the fact that cannabinoids mediate GABA release in interneuron networks suggests that one of the functions of the CB1R is to maintain optimal

excitatory–inhibitory balance that would be particularly relevant in brain regions with a high density of CB1Rs. Thus, acute and chronic exposure to exogenous cannabinoids would disrupt this balance, leading to altered inhibitory tone, with downstream perturbations in functionally relevant gamma (and perhaps theta) oscillations.

In terms of potential mechanisms whereby chronic cannabinoids may disrupt endocannabinoid dynamics, several possibilities exist. First, as THC competes with endocannabinoid transmitters at the CB1R, recent cannabis exposure may cause a compensatory increase in the synthesis and release of endocannabinoids such as anandamide and 2-arachidonoyl glycerol (2-AG). Indeed, a recent study in humans demonstrated that a single oral dose of 20 mg THC resulted in significant increases in anandamide, 2-AG, palmitoyl ethanolamide, and oleoylethanolamide for several hours after administration (Walter *et al*, 2013). This
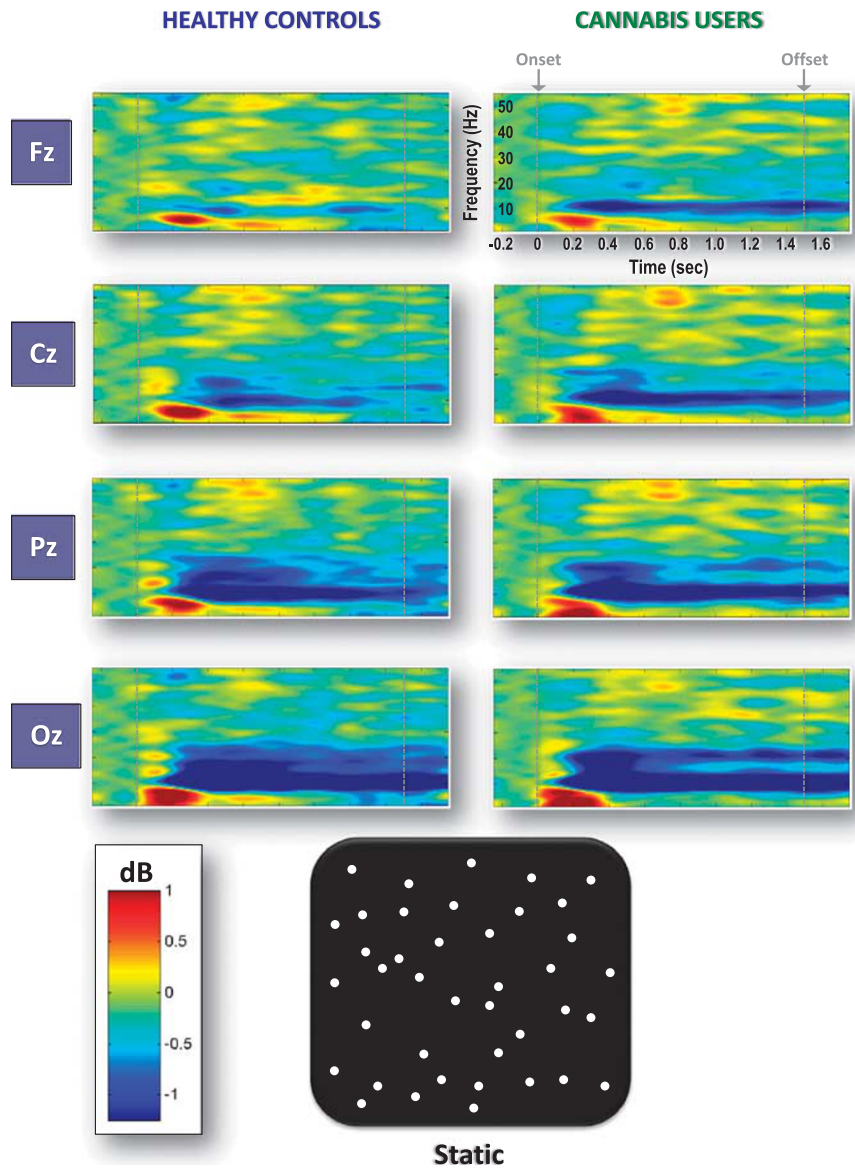
Figure 3 Grand-averaged time × frequency plots demonstrating mean trial power (MTP) for midline electrodes during the static condition for the healthy control and cannabis groups.

effect was corroborated in a second experiment in rats with the synthetic cannabinoid WIN-55,212 (Walter *et al*, 2013). However, the fact that the present study examined induced gamma oscillations at a mean of 42.9 h after last cannabis exposure makes this mechanism unlikely. A second possibility is that chronic cannabis exposure produced significant CB1R downregulation in the cannabis group. Support for this notion comes from previous animal and human studies that have shown that chronic exposure to exogenous cannabinoids decreases the level of CB1Rs, an effect that can last for days to a week (Ceccarini *et al*, 2013; Hirvonen *et al*, 2012; Sim-Selley, 2003). Such decreases in CB1Rs could lead to alterations in GABA release, thus disrupting the ability of neural networks to generate synchronized neural oscillations. Indeed, a transcranial magnetic stimulation (TMS) study by Fitzgerald *et al* (2009) found that both heavy and light users of cannabis exhibit

disruptions in short interval cortical inhibition that is indicative of altered GABA function. A final potential mechanism relates to the effect of cannabis on neurodevelopment. It is now well established that the endocannabinoid system plays a significant role in neurogenesis, neural specification, neural maturation, neuronal migration, axonal elongation, and glia formation (Harkany *et al*, 2007, 2008a, b). Furthermore, CB1R levels peak in adolescence, suggesting that young cannabis users may be particularly vulnerable to the development-altering effects of cannabis (Ellgren *et al*, 2008; Heng *et al*, 2011). In support of this idea, cannabis-related decreases in steady-state gamma power have been shown to be more profound in individuals who start using cannabis at an earlier age (Skosnik *et al*, 2012). Furthermore, a recent animal study demonstrated that chronic exposure to THC or WIN during adolescence permanently disrupted the ability to generate cortical
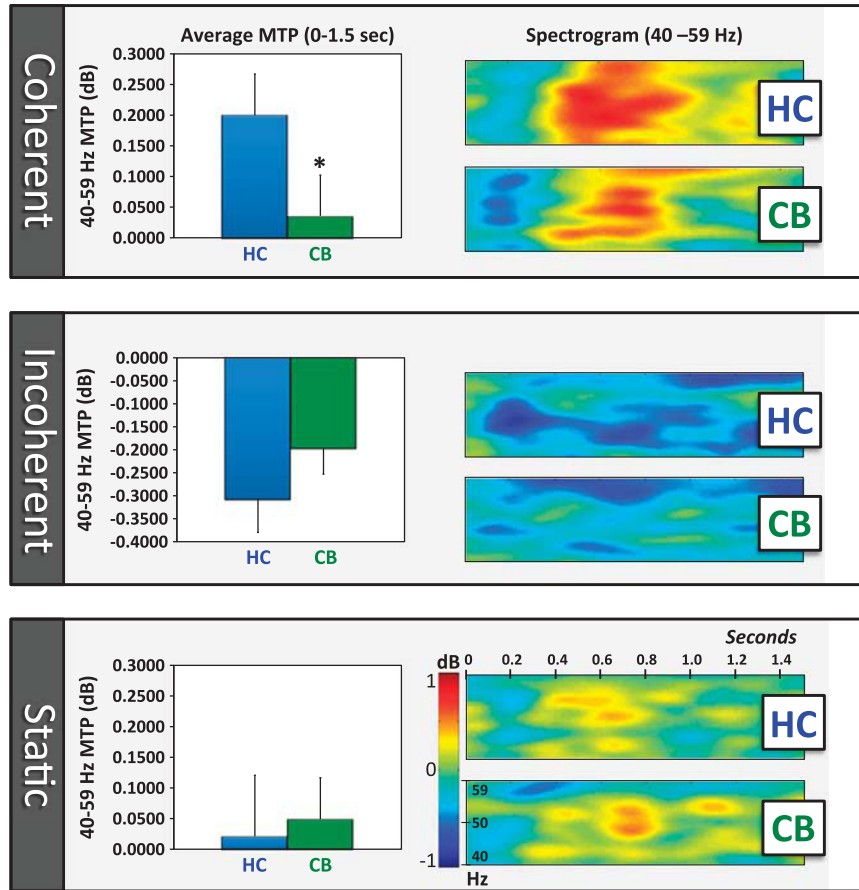
Figure 4 (Left) Average mean trial power during the period of stimulation (0–1.5 s) for each of the three experimental conditions for the healthy control (HC) and cannabis (CB) groups (data from electrode Cz). Cannabis users demonstrated decreased gamma power (40–59 Hz) in the coherent motion condition compared with healthy controls (top). (Right) Time × frequency spectrograms illustrating MTP from 40 to 59 Hz in each experimental condition for the control and cannabis groups (electrode Cz).
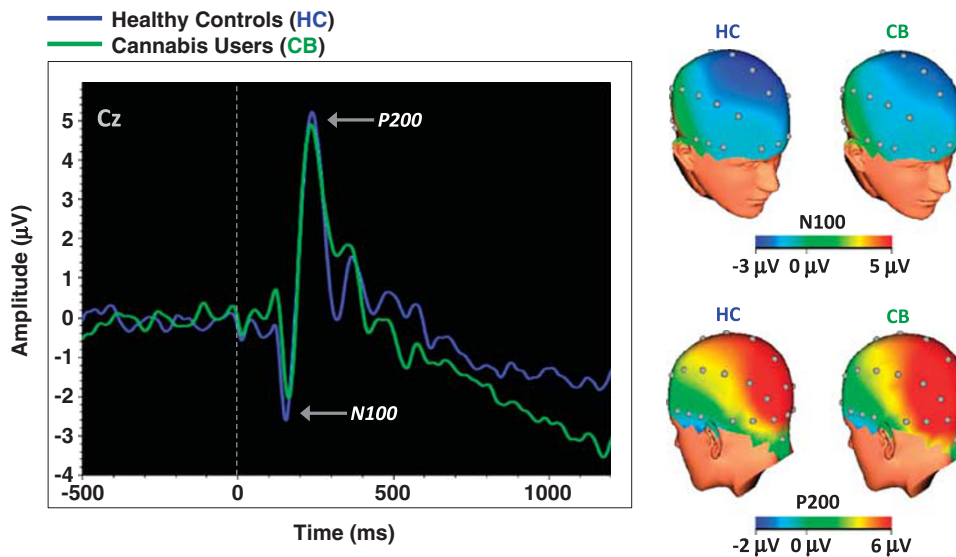

Figure 5 (Left) Grand-averaged ERPs to stimulus onset (N100–P200) at electrode Cz for the healthy control (HC) and cannabis (CB) groups during the coherent motion condition. No differences were found between the groups in N100–P200 in any of the experimental conditions, indicating normal primary visual processing. (Right) Grand-topographic maps for the N100 (top) and P200 (bottom) for healthy controls and cannabis users from the coherent motion condition.
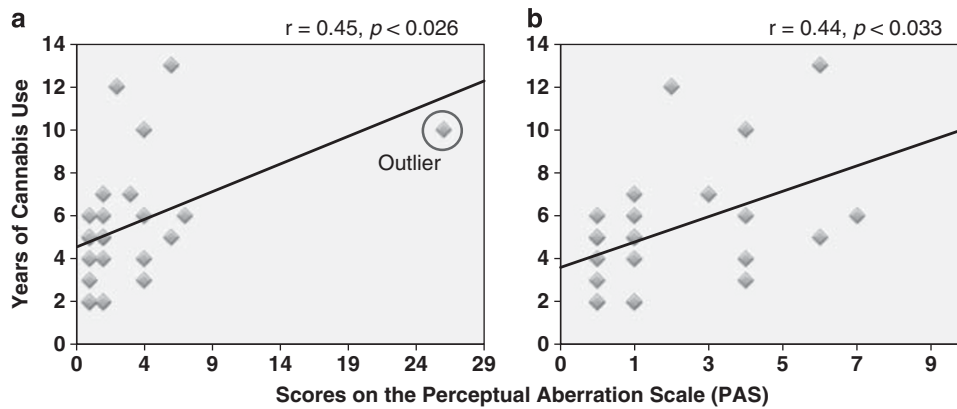
Figure 6 (Left) Correlation between PAS scores and total years of cannabis use. (Right) Correlation between PAS scores and total years of cannabis use after the removal of outlier.

oscillations in several frequencies (including gamma) when tested in adulthood. This effect was not observed in a comparison group in which THC and WIN was administered only in adult animals (Raver et al, 2013). Hence, earlier cannabis exposure during adolescence may alter neurodevelopmental trajectories that could permanently perturb the cortical 'machinery' necessary in the generation of synchronized oscillations.

Several limitations in the current study need to be addressed. First, there has been some debate as to whether visually induced gamma activity is neural in origin (Fries et al, 2008; Yuval-Greenberg et al, 2008). For example, Yuval-Greenberg et al (2008) reported that visually induced gamma correlated with miniature saccades, and such activity lasted for < 200 ms (Yuval-Greenberg et al, 2008). However, in the current study, the induced gamma activity was observed continuously for over 500–1000 ms, and this is close to the entire period of the stimulation. It is known that microsaccades occur at low frequency (< 1 Hz) (Martinez-Conde et al, 2009), and it is therefore unlikely that the induced gamma activity seen in the current study was influenced by microsaccades. Finally, activity from microsaccades is typically observed in frontal electrode sites, and the induced gamma observed here was largest at in centroparietal sites as in previous work from our group (Krishnan et al, 2005).

A second limitation is the cross-sectional nature of the experimental design that makes determining exact cause and effect relationship difficult. Hence, the observed effects could be because of residual THC, CB1R downregulation, cannabis withdrawal, or neurodevelopmental changes in cannabis users. Third, the cannabis plant contains nearly 70 phytocannabinoids, and hence it unclear what specific constituent plays a role in disrupting induced gamma oscillations. These limitations could partially be addressed in future studies by examining gamma oscillations in the context of acute cannabinoid administration in humans. Fourth, the limited age range of the sample raises questions about the generalizability of the current findings. Finally, although the cannabis group reported no other illicit drug use in the past 3 months, it is possible that the use of other substances in the remote past contributed to the findings. These limitations notwithstanding, the current data suggest that chronic exposure to cannabinoids may alter the ability

to generate neural oscillations in the gamma range during Gestalt visual perception, and this may have implications for understanding the short- and long-term neurobehavioral effects of cannabis.

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