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Acute separate and combined effects of cannabinoid and nicotinic receptor agonists on MMN-indexed auditory deviance detection in healthy humans

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ABSTRACT

The high prevalence of concomitant cannabis and nicotine use has implications for sensory and cognitive processing. While nicotine tends to enhance function in these domains, cannabis use has been associated with both sensory and cognitive impairments, though the underlying mechanisms are unclear. Additionally, the interaction of the nicotinic (nAChR) and cannabinoid (CB_1) receptor systems has received limited study in terms of sensory/cognitive processes. This study involving healthy volunteers assessed the acute separate and combined effects of nabilone (a CB_1 agonist) and nicotine on sensory processing as assessed by auditory deviance detection and indexed by the mismatch negativity (MMN) event-related potential. It was hypothesized that nabilone would impair auditory discriminability as shown by diminished MMN amplitudes, but not when administered in combination with nicotine. 20 male non-smokers and non-cannabis-users were assessed using a 5-stimulus 'optimal' multi-feature MMN paradigm within a randomized, placebo controlled design (placebo; nabilone [0.5 mg]; nicotine [6 mg]; and nicotine + nabilone). Treatment effects were region- and deviant-dependent. At the temporal regions (mastoid sites), MMN was reduced by nabilone and nicotine separately, whereas co-administration resulted in no impairment. At the frontal region, MMN was enhanced by co-administration of nicotine and nabilone, with no MMN effects being found with separate treatment. These neural effects have relevance for sensory/cognitive processes influenced by separate and simultaneous use of cannabis and tobacco and may have treatment implications for disorders associated with sensory dysfunction and impairments in endocannabinoid and nicotinic cholinergic neurotransmission.

1. Introduction

Tobacco and cannabis are widely consumed substances which exert modulatory influences on cognitive and behavioural systems, yet the neurobiological mechanisms underlying such alterations with separate or combined use are not fully understood. Nicotine, the primary psychoactive component in tobacco smoke, acts as a full agonist of nicotinic acetylcholine receptors (nAChR) which are widely distributed throughout the brain, including in regions regulating reward/addiction and cognition (Jasinka et al., 2014). Although cognitive improvement with nicotine and nAChR agonist treatment strategies is not found in all studies, acute nicotine and nAChR agonist administration has been shown to enhance sensory/perceptual, attentional, mnemonic, and executive functions (Levin and Simon, 1998; Levin et al., 2006). These behavioural and neural effects often appear in an 'inverted-U shaped' pattern of nicotinic influences by which the direction of change varies with dose, age, smoker vs. non-smoker status, and smoking abstinence state (Newhouse et al., 2004, 2011; Picciotto, 2003).

Cannabis is the most prevalent illicit drug used in the Western world, and although the effects of chronic, long-term cannabis use on cognition and behavioural systems are controversial (Cohen and Weinstein, 2018; Gonzalez et al., 2017), laboratory studies in healthy individuals have shown the acute transient dose-response effects of cannabinoids (i.e., cannabis, the active cannabis ingredient Δ 9-

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tetrahydrocannabinol [THC], or the synthetic analog nabilone) to impair a range of neurocognitive systems, including executive, emotional, and memory processing. These deficits differ in severity depending on several factors including the type of drug, dose, and age (Calabrese and Rubio-Casillas, 2018; Cohen and Weinstein, 2018; Gorey et al., 2019).

Interacting with the endogenous cannabinoid (endocannabinoid) system, the psychoactive effects of cannabis are primarily mediated by THC, serving as a partial agonist at presynaptic type 1 receptors (CB_1Rs), which are found throughout the brain, with highest concentrations in regions (hippocampus, prefrontal cortex, amygdala, cerebellum, basal ganglia) that regulate the expression of cognitive and emotional behaviours (Kano et al., 2009; Kaur et al., 2016; Lu and Mackie, 2016). CB_1Rs are activated by acute and repeated dosing with exogenous cannabinoids (Bloomfield et al., 2019; Sagar and Gruber, 2018) and exhibit a global reduction in cerebral availability in chronic cannabis users (Ceccarini et al., 2015).

Compared to co-use of other substances (Agrawal et al., 2012; Coffey et al., 2003; Margolese et al., 2004), tobacco and cannabis are often used in combination, with 41–94% of cannabis users smoking tobacco at some point in their lives (e.g., (Agrawal and Lynskey, 2009), while 25–52% of young adult (15–24 years) tobacco smokers report using cannabis (e.g., (Leatherdale et al., 2007). Recent trends indicate that while cannabis use has increased in tobacco users, tobacco use has declined among cannabis users (Schauer et al., 2015). Co-occurring (i.e., concurrent or simultaneous) cannabis and tobacco users report greater cannabis consumption, more severe psychosocial consequences (Peters et al., 2012), and are more likely to meet criteria for mental health disorders (Peters et al., 2014). A number of potential theories and mechanisms, including synergistic and compensatory effects of co-use, have been proposed to explain co-morbid cannabis and tobacco use (Rabin and George, 2015; Viveros et al., 2006). Given the extensive overlap of CB_1Rs and nAChRs in brain regions mediating sensory and cognitive processes, it is important that we further our neurobiological understanding of cannabis-tobacco interactions as they pertain to sensory/cognitive functions.

In the realm of cognition, the electroencephalographically (EEG) derived mismatch negativity (MMN) event-related brain potential (ERP) is considered an electrophysiologic endophenotype of basic, low-level sensory processing (Light et al., 2010) that has a direct (mediating) effect on cognition (Thomas et al., 2017). The auditory MMN is commonly used to study the neural correlates of early sensory processing and requires no behavioural response or attention, and reflects the function of the auditory "echoic" sensory memory system, which maintains brief representations of auditory stimulus features (Näätänen et al., 2007). The MMN is automatically elicited when a sequence of repetitive "standard" stimuli is interrupted infrequently by "deviant" stimuli differing with respect to physical (e.g. sound intensity, duration, pitch, etc.) or abstract (e.g. sound pattern or complex sequential stimulus role) features (Naatanen et al., 2004). The MMN, a subtraction-based waveform (deviant-standard stimuli) with a frontocentral peak occurring at ~120–250 ms post-deviant onset, is thought to signal a *predication-error* based on regularity violation. The resulting MMN is thus believed to indicate that the sensory memory model has failed to account for the current sensory input (Todd et al., 2013). Modulated primarily by glutamatergic *N*-methyl-D-aspartate (NMDA) receptor activity (Rosburg and Kreitschmann-Andermahr, 2016), the MMN is believed to be generated by a temporofrontal network, with bilateral auditory-cortex activation, responsible for pre-perceptual deviance detection (the supratemporal MMN subcomponent), eliciting a primarily right frontal hemispheric frontal process, which is responsible for an involuntary attention switch to the auditory deviance (the frontal MMN subcomponent) (Näätänen et al., 2011).

In healthy volunteers, although both non-significant (Knott et al., 2011; Knott et al., 2006) and diminishing amplitude effects have been observed with the pitch deviant MMN following acute nicotine administration (Knott et al., 2009), this frontal MMN has generally been found to exhibit a shortened latency (Inami et al., 2007, Inami et al., 2005) and/or an increased amplitude with nicotine or selective nAChR agonist treatment (Dunbar et al., 2007; Harkrider and Hedrick, 2005). Nicotine has also enhanced MMN elicited by auditory pattern (Baldeweg et al., 2016), temporal (Martin et al., 2009) and intensity and double deviants (Hamilton et al., 2018) as well as by visual deviants (Fisher et al., 2010). Duration MMN has been reduced by nicotine (Mathalon et al., 2014) but it and other MMNs elicited at frontal electrodes by different classes of deviants have been shown to be both increased and decreased by nicotine and nAChR agonist administration depending on initial baseline amplitude (Knott et al., 2014, 2015; Smith et al., 2015). Variability in these findings across studies may be related to nicotine dose and smoker vs. non-smoker status.

Concerning cannabis effects, acute oral administration of cannabis extract (containing THC and cannabidiol [CBD]) but not THC alone significantly increased pitch MMN amplitudes not at frontal but at central scalp electrodes (which are more proximal to temporal/auditory cortex generators), and central scalp amplitude increases were negatively correlated with plasma levels of the THC metabolite 11-OH-THC (Juckel et al., 2007). In the only other acute study, involving a glutamatergic model of SZ, co-administration of the CB_1R agonist rimonabant with the NMDA-receptor antagonist ketamine decreased amplitude of the frontal MMN elicited by a duration (but not pitch) deviant, an effect not seen with ketamine alone and thus implicating a disturbed interaction between endocannabinergic and glutamatergic neurotransmission in MMN dysfunction in SZ (Roser et al., 2011).

Undoubtedly cannabis and tobacco use are linked and evidence suggests that they may exert contrasting effects on cognition, including the neural processing of deviant auditory sensory information indexed by MMN. While there is a need to understand the neurobiological factors that facilitate the relationship between the co-use of these substances, to date there are no brain-based human studies evaluating the simultaneous use of cannabis and tobacco on neural correlates of early auditory information processing. The primary objective of this study, conducted in healthy volunteers, is to examine the separate and combined effects of the CB_1R inverse agonist nabilone and the nAChr agonist nicotine on pre-attentive auditory deviance detection as measured by MMN. Given previous findings suggesting that activation of nAChR and CB_1R systems may differentially affect MMN depending on deviant type and cortical region, MMN will be elicited within an 'optimal' stimulus paradigm involving five auditory deviants and will be assessed from frontal and temporal (mastoid) scalp recording sites. As both repeated use of and abstinence from cannabis and tobacco may induce long-term neuroadaptive changes in cannabinoid and nicotinic receptor signaling and therefore potentially moderate acute response to CB_1R and nAChR agonists, these potential confounds will be limited in this study by employing a sample of non-tobacco and non-cannabis using participants. NMDA receptor activity has been implicated in MMN generation (Rosburg and Kreitschmann-Andermahr, 2016), and cannabis and tobacco exert opposing modulatory effects on glutamatergic neurotransmission, depressing and increasing glutamate release, respectively (Colizzi et al., 2016; Koukouli and Masko, 2015). Accordingly, we generally expect that, across deviant types and recording regions, acute treatment with the CB_1R agonist nabilone will attenuate MMN while nAChR agonist treatment with nicotine will enhance MMN, and block the dampening actions of nabilone on MMN generation during co-administration.

2. Method

The study protocol was approved by the Research Ethics Boards of the Royal Ottawa Health Care Group and the University of Ottawa and was carried out in accordance with the Canadian Tri-Council Policy Statement for Ethical Conduct for Research Involving Humans. All volunteers provided written consent prior to participation and were compensated $200 CAD for their time and effort.

2.1. Participants

Twenty right handed, non-smoking, healthy male volunteers with a mean age of 23.6 years (SD = 4.0) were recruited from the local community (primarily from universities via word of mouth) to participate in the study. Only right-hand dominant individuals were chosen to reduce inter-individual variability in hemispheric lateralization of acoustic cues evidenced with MMN (Gu et al., 2013). Only males were recruited in order to rule out any potential confounding effects of menstrual cycle phases which may be expressed in a repeated-measures design. Volunteers were initially screened by telephone and then by personal interview. Based on history and physical exam, all participants were medically and neurologically normal and, as screened with the SCID-NP (Structured Clinical Interview - Non-Patient version for DSM-IV (Williams et al., 1992) and FIGS (Family Interview for Genetic Studies: (Maxwell, 1992), had no personal or immediate (first degree biological relatives) family history of psychiatric disorders, including alcohol/substance abuse and dependence. Participants were non-smokers (less than 100 cigarettes in their lifetime and none in the past year), were non-users of cannabis (less than 10 joints in a lifetime, none in the past year), had no history of drugs/alcohol abuse and exhibited normal hearing as assessed by audiometric testing. Testing for recent cannabis exposure was carried out by urine analysis (Innovacon *E*-Z Split Key Cup Drug Screen Test Panel), and recent smoking exposure was assessed by analysis of expired air carbon monoxide (CO) level, which was required to be below 3 ppm (ppm), a level consistent with non-smoking status (Cropsey et al., 2006).

2.2. Design

Participants were assessed in a randomized, double-blind, placebo-controlled, within-subjects (repeated measures) design consisting of 4 test sessions involving administration of nabilone, nicotine, nabilone plus nicotine and placebo, with a minimum of 3 days between sessions. Assessments were carried out at the expected time, based on previous literature of known pharmacokinetics, drugs reach maximal blood level concentrations (T_{max}).

2.3. Treatments

Nabilone (Cesamet® capsules) is a synthetic cannabinoid receptor agonist (manufacturer Valeant Canada Ltd) approved by Health Canada for human use in treatment of symptoms such as nausea and vomiting. Nabilone, a THC analog, is typically administered in doses ranging between 1 and 2 mg twice per day and blood nabilone levels peak at ~ 2 h (T_{max}). For the purpose of this study, a minimum dose of 0.5 mg was administered to the participants to reduce possible adverse events and participant attrition associated with higher doses. The placebo capsule was composed of cellulose, and was physically identical to the active capsule.

Nicotine was administered orally as two pieces cinnamon-flavoured polacrix gum; one piece was a 2-mg Nicorette® polacrix gum and the other a 4-mg Nicorette Plus® for a total dose that was expected to produce a maximum peak nicotine blood concentration between 16 and 26 ng/ml after a 20 min (T_{max}) chewing period. This value is comparable to 15–30 ng/ml, which is typically found after smoking of a single cigarette of medium nicotine yield (Hukkanen et al., 2005). The placebo consisted of two pieces of commercially available cinnamon-flavoured gum, which were similar to nicotine gum in size, color, and shape. During gum administration, the participants were required to wear a nose plug and a blindfold to reduce visual and sensory differences between the nicotine and placebo gums. Gums were chewed according to manufacturer's guideline tape which includes biting gum twice per minute and keeping gum 'parked' between teeth and cheek between bites. Following the end of the tape, participants were given a commercially available flavoured gum to chew for about 2 min in order to mask any remaining differences between the nicotine and placebo gums.

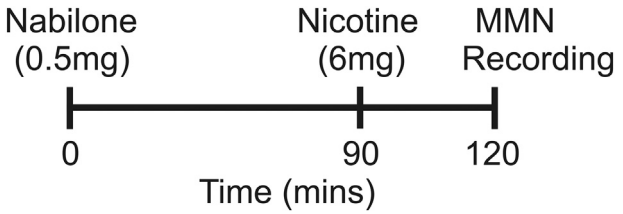

Fig. 1. Schematic timeline of drug administration and MMN recording.

As T_{max} for Nicorette® is 20–30 min, it was administered 90 min after nabilone to ensure approximately simultaneous plasma level peaks of both drugs during the treatment combination session. This staggered administration procedure was carried out for each session. To maintain study blind, a double-dummy administration procedure was used by administering two gum pieces and a capsule during each test session (e.g., nicotine treatment = 4 mg nicotine +2 mg nicotine + placebo capsule). Fig. 1 displays the timeline of drug administration.

2.4. Procedures

Test sessions occurred in the morning (8–11 a.m.) following overnight abstinence of drugs, alcohol, caffeine and food. Session procedures occurred in a fixed sequence beginning with treatment administration, a 2 h absorption period, and then administration of the mismatch-negativity (MMN) paradigm. Adverse events rated by the participants were analyzed for safety purposes only.

2.5. Paradigm

During the MMN paradigm participants viewed a silent video (The Blue Planet by BBC, 2001). In the optimal MMN paradigm (Naatanen et al., 2004), auditory tonal stimuli of 70 dB sound pressure level (SPL) were presented binaurally through headphones and consisted of standard (p = .5) stimuli (composed of three sinusoidal partials of 500, 1000, and 1500 Hz, 75 ms duration) that were randomly intermixed with deviant (p = .5) stimuli. Stimulus onset asynchrony (SOA) was fixed at 500 ms. The deviant tones differed from the standard tones in terms of frequency, duration, intensity, perceived location of sound origin, or contained a silent gap in the middle of the tone (i.e. gap deviants). The duration deviant was only 25 ms in duration (instead of 75 ms). Half of the frequency deviants were 10% lower (composed of 450, 900, and 1350 Hz partials) and the other half were 10% higher (composed of 550, 1100, and 1650 Hz partials). Half of the intensity variants were at 80 dB and the other half at 60 dB. A change in perceived location was created by creating an 800 μs time difference between the channels, leading to a change in location of approximately 90°. Half of the deviants had a 800 μs delay in the right channel while the other half was in the left channel. In the gap deviants 7 ms (including a 1 ms rise and fall) were removed from the middle of the standard stimulus. Stimuli were presented in 3 sequences of 5 min each (1845 stimuli) for a total of 15 min (5535 stimuli). Each sequence started with a 15 standard tones, followed by a sequence in which every second tone was a standard (p = .5) and every other tone was one of the five deviants (p = .1 each). One deviant of each category was presented once every five deviants and deviants of the same category were never presented consecutively.

2.6. ERPs

ERPs were recorded with a cap embedded with Ag^+/Ag^+Cl^- electrodes (EasyCap, Herrching-Brieibrunn, Germany) positioned on 8 scalp locations, including left, right, and middle frontal (F3, F4, Fz); left

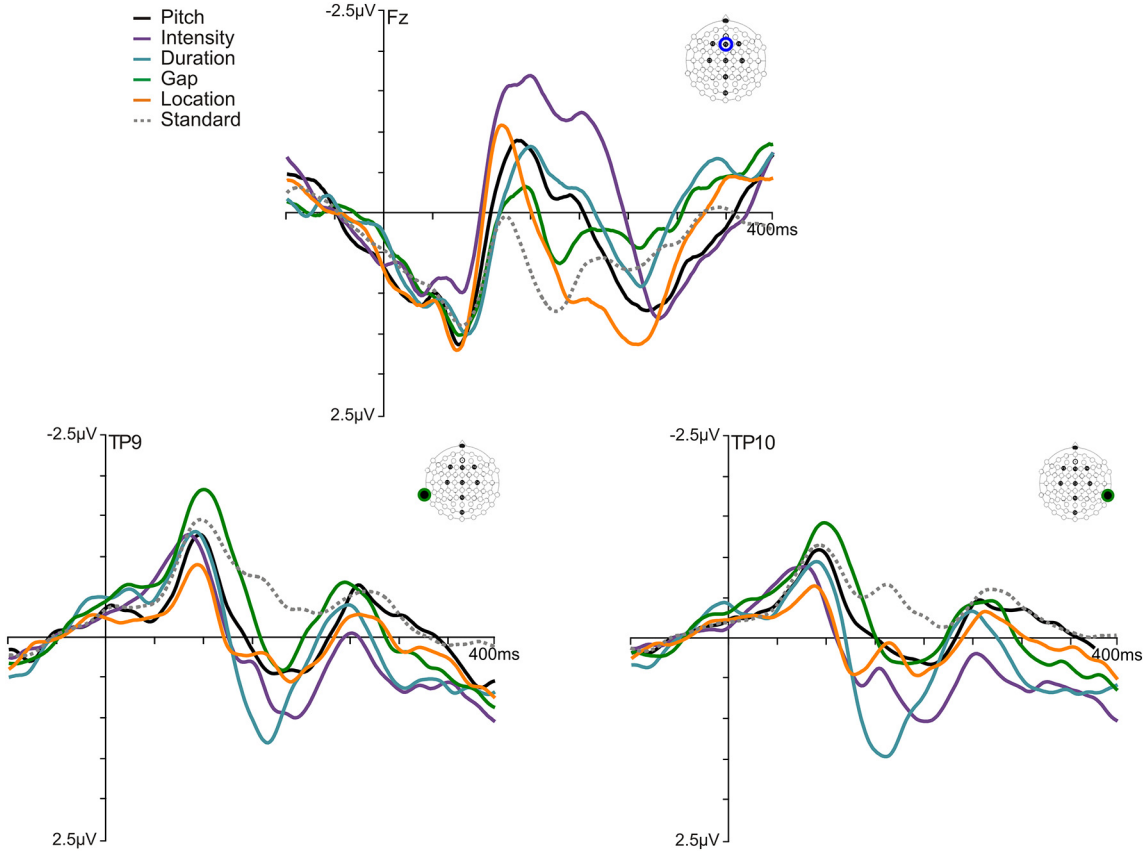

Fig. 2. Grand averaged ERP waveforms (for placebo condition) showing response to standard and each deviant stimulus at mid-frontal (Fz) and left (TP9) and right (TP10) temporal (mastoid) scalp sites.

and right temporal (TP9, TP10); and middle central (Cz), parietal (Pz) and occipital (Oz) sites, according to the 10–10 system (Chatrian et al., 1985). An electrode on the nose served as reference and a ground electrode was positioned above the F_Z site. Electrodes were placed above and below the right eye to record vertical electrooculographic (VEOG) activity and at the external canthus of both eyes to measure horizontal electrooculographic (HEOG) activity. Electrical recordings were carried out using a Brain Vision V-8 Amp® (Brain Products GmbH, Munich, Germany) amplifier and Brain Vision Recorder® (Brain Products GmbH, Munich, Germany) software. Electrical activity was sampled at 500 Hz, with amplifier bandpass filters set at 0.1–100.0 Hz. Electrode impedances were kept below 5 kΩ.

Off-line analysis was performed with Brain Vision Analyzer® software (Brain Products, GmbH, Munich, Germany). For each stimulus, electrical epochs of 500 ms duration (beginning 100 ms prior to stimulus onset) were digitally filtered (0.1–20 Hz) (Sabri and Campbell, 2002), ocular (Gratton et al., 1983) and baseline corrected (relative to the pre-stimulus segment), and only epochs with EEG voltages below 75 μV were used for final ERP averages, which were constructed separately for the standard and each deviant stimulus type at each electrode site. Waveforms for the low and high frequency deviants, those for the low and high intensity deviants, and those for the right and left location, were averaged together.

MMNs were analyzed with difference waveforms, which were derived by digital point-by-point subtraction of the standard stimulus values from those elicited by each of the deviant stimuli. MMN amplitude was defined as the most negative peak (± 5 ms) between 120 and 250 ms at the frontal electrodes (F3, Fz, F4) and as the most positive peak at the mastoid sites (TP9, TP10), where the MMN is inverted in voltage polarity (when processed with a nose reference), reflecting the orientation of the dipole generator of the MMN originating in the auditory cortex and directed toward frontal cortex regions. Amplitude of the N1 component (peak negativity between 90 and 120 ms) elicited by the standard stimulus was also measured (from Fz).

2.7. Adverse events

Adverse events were evaluated by having participants complete a 5-point Likert scale (0 = none, 4 = severe) on common physical (e.g., jitteriness, headache, nausea, fatigue, heart palpitations) and psychological symptoms (e.g., high feeling, anxious, relaxed, agitated) associated with nicotinic and cannabinoid stimulation (adapted from Harkrider and Hedrick, 2005).

2.8. Statistical analysis

Statistical analysis was carried out using the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). Separate mixed Analysis of Variances (ANOVA) for amplitude elicited by each deviant type measure were carried out for frontal and mastoid sites separately. The mid-frontal (Fz) site ANOVA consisted of one within-group factor with four levels (nicotine, nabilone, nicotine plus nabilone, placebo). The mastoid sites ANOVA contained two within-group factors, including treatment with four levels and electrode site with two levels (left [TP9], right [TP10]). MMN latency (at Fz only for the frontal MMNs and at TP9 and TP10 for the mastoid MMNs) was analyzed with similar ANOVAs but with no site factor for the frontal MMN analysis. Significant (Greenhouse-Geisser corrected where appropriate) effects were followed up with Bonferroni-adjusted comparisons using separate (vs. pooled) error estimates. Adverse events were analyzed with one-way ANOVAs.

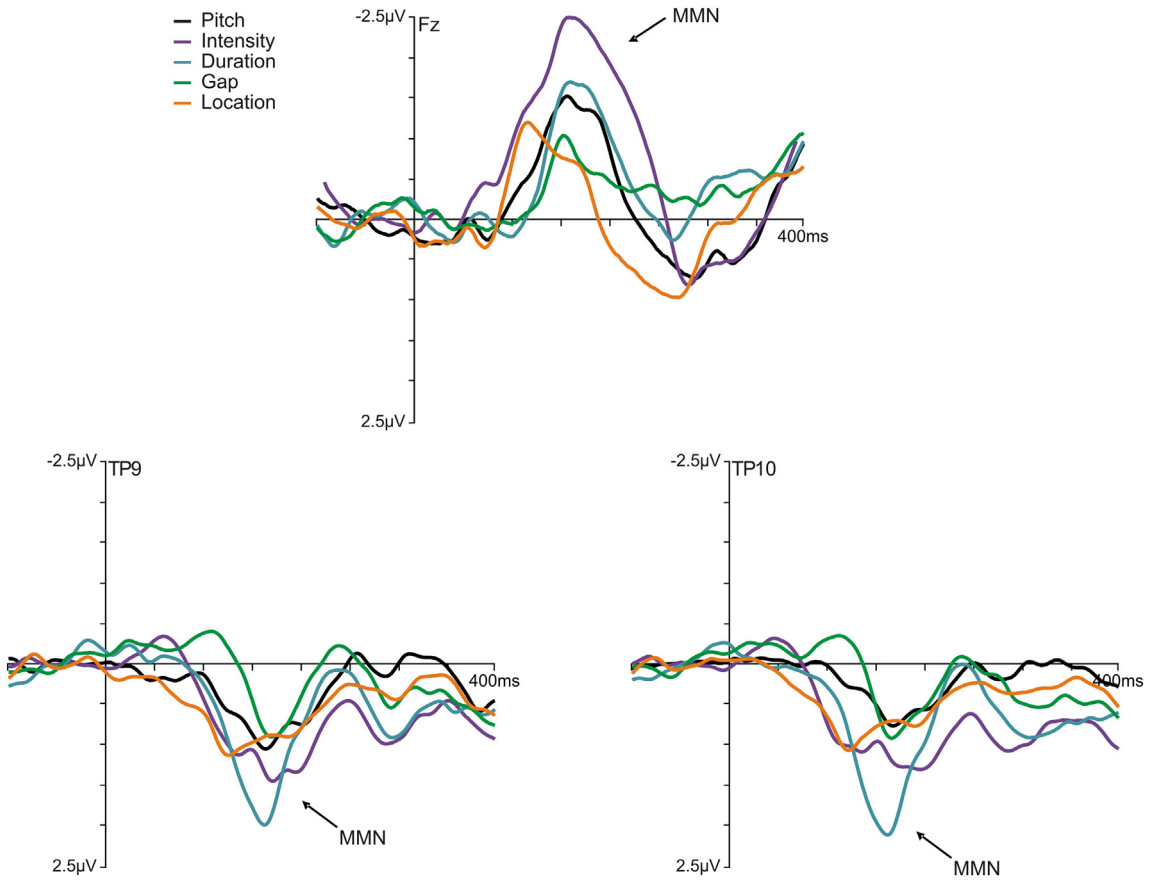

Fig. 3. Grand averaged difference MMN waveforms for placebo condition obtained from mid-frontal (Fz) and left (TP9) and right (TP10) temporal (mastoid) scalp sites.

3. Results

All study participants completed the four test sessions without experiencing any adverse events. Grand average raw waveforms for the placebo session are shown in Fig. 2 and the difference waveforms are displayed in Fig. 3.

3.1. Frontal MMNs

Grand average difference waveforms for each deviant at the frontal electrode site (Fz) during each treatment session are displayed in Fig. 4.

3.1.1. Duration deviant

Analysis did not yield any significant main effect for the duration deviant [$F(3,57) = 0.98$, $p > .05$], with the placebo ($M = -2.14\,\mu V$, S.E. ± 0.38), nabilone ($M = -2.62\,\mu V$, S.E. ± 0.38), nicotine ($M = -2.11\,\mu V$, S.E. ± 0.38), and combination ($M = -2.41\,\mu V$, S.E. ± 0.36) treatment showing no MMN amplitude differences.

3.1.2. Frequency deviant

Analysis did not yield any significant main effect for the frequency deviant [$F(3,57) = 0.74$, $p > .05$], with the placebo ($M = -1.81\,\mu V$, S.E. ± 0.36), nabilone ($M = -2.19\,\mu V$, S.E. ± 0.30), nicotine ($M = -1.94\,\mu V$, S.E. ± 0.25), and combination ($M = -2.23\,\mu V$, S.E. ± 0.31) treatments showing no MMN amplitude differences.

3.1.3. Gap deviant

No significant main effect was observed for the gap deviant [$F(3,57) = 0.93$, $p > .05$], with the placebo ($M = -1.37\,\mu V$, S.E. ± 0.31), nabilone ($M = -1.43\,\mu V$, S.E. ± 0.33), nicotine ($M = -1.21\,\mu V$, S.E. ± 0.31), and combination ($M = -1.42\,\mu V$, S.E. ± 0.27) treatment showing similar amplitudes.

3.1.4. Intensity deviant

Analysis yielded no significant main effect for the intensity deviant [$F(3,57) = 0.57$, $p > .05$], with the placebo ($M = -2.99\,\mu V$, S.E. ± 0.29), nabilone ($M = -2.87\,\mu V$, S.E. ± 0.34), nicotine ($M = -2.64\,\mu V$, S.E. ± 0.23), and combination ($M = -2.68\,\mu V$, S.E. ± 0.27) treatment evidencing equivalent amplitudes.

3.1.5. Location deviant

A significant main effect of treatment was observed [$F(3,57) = 2.94$, $p = .04$], with the combination treatment ($M = -2.46\,\mu V$, S.E. ± 0.33) significantly increasing MMN amplitudes ($p = .01$) compared to placebo ($M = -1.41\,\mu V$, S.E. ± 0.19) but not to nicotine ($M = -1.90\,\mu V$, S.E. ± 0.39) or nabilone ($M = -1.64\,\mu V$, S.E. ± 0.31) treatment.

3.2. Mastoid MMNs

Grand average difference waveforms for each deviant at the left and right temporal electrode sites (TP9, TP10) are displayed in Fig. 5.

3.2.1. Duration deviant

Analysis did not show any significant main effect of electrode site [$F(1,19) = 0.27$, $p > .05$] or treatment x electrode interaction effects [$F(3,57) = 0.11$, $p > .05$] for the duration deviant but revealed a main effect of treatment [$F(3,57) = 3.59$, $p = .02$]. Across left and right temporal sites, the placebo ($M = 2.18\,\mu V$, S.E. ± 0.31) MMN was significantly ($p = .04$) greater than the nabilone condition ($M = 1.48\,\mu V$, S.E. ± 0.18) and significantly ($p = .03$) greater than the nicotine condition ($M = 1.27\,\mu V$, S.E. ± 0.35). MMN in the combination

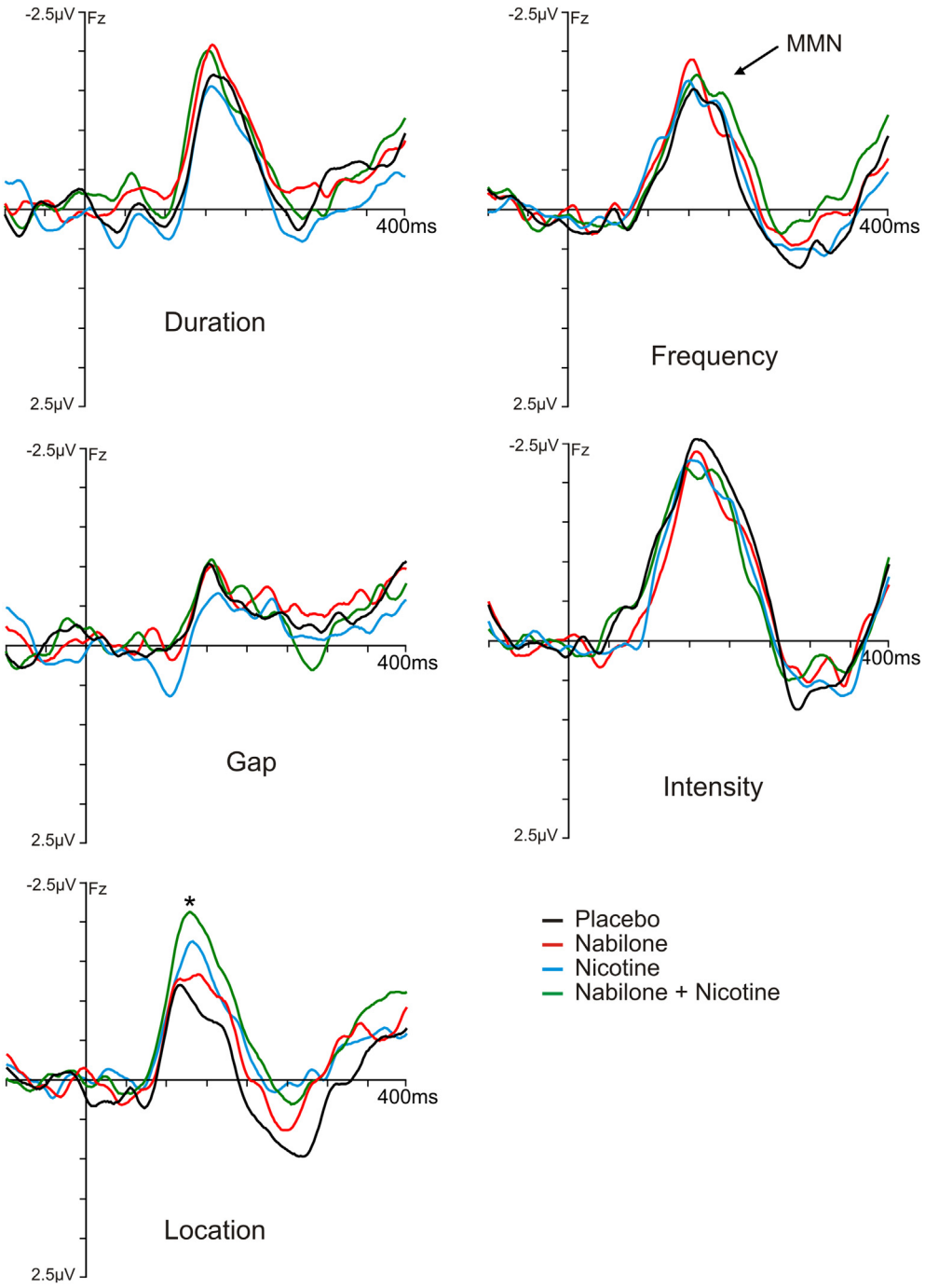

Fig. 4. Grand averaged difference MMN waveforms recorded at mid-frontal (Fz) scalp site for each deviant and each treatment session. * $p < .05$.

(M = 2.08 μV, S.E. ± 0.19) treatment was also significantly greater than MMN in the nabilone ($p = .04$) and the nicotine ($p = .04$) conditions but was similar to the MMN in the placebo condition. No differences in MMN were found between the nicotine and nabilone conditions.

3.2.2. Frequency deviant

No significant treatment [$F(3,57) = 1.01$, $p > .05$], electrode site [$F(1,19) = 2.71$, $p > .05$] or treatment x electrode interaction effects [$F(3,57) = 0.24$, $p > .05$] were found for the frequency deviant, with MMN amplitudes across temporal sites being similar for placebo (M = 1.24 μV, S.E. ± 0.34), nabilone (M = 1.06 μV, S.E. ± 0.18), nicotine (M = 1.10 μV, S.E. ± 0.28) and combination treatment (M = 1.56 μV, S.E. ± 0.22) conditions.

3.2.3. Gap deviant

Analysis failed to show any significant treatment [$F(3,57) = 1.63$, $p > .05$], electrode site [$F(1,19) = 0.73$, $p > .05$] or treatment × electrode interaction effects [$F(3,57) = 1.41$, $p > .05$] for the gap deviant, which elicited equivalent averaged temporal MMN amplitudes to placebo (M = 1.05 μV, S.E. ± 0.29), nabilone (M = 1.03 μV, S.E. ± 0.25), nicotine (M = 0.82 μV, S.E. ± 0.31), and treatment combination (M = 1.01 μV, S.E. ± 0.22) conditions.

3.2.4. Intensity deviant

Analysis did not show any significant electrode site [$F(1,19) = 0.42$, $p > .05$] or treatment × electrode site interaction effects [$F(3,57) = 2.09$, $p > .05$] for the intensity deviant, but observed a main effect of treatment [$F(3,57) = 2.95$, $p = .04$]. MMN in the placebo

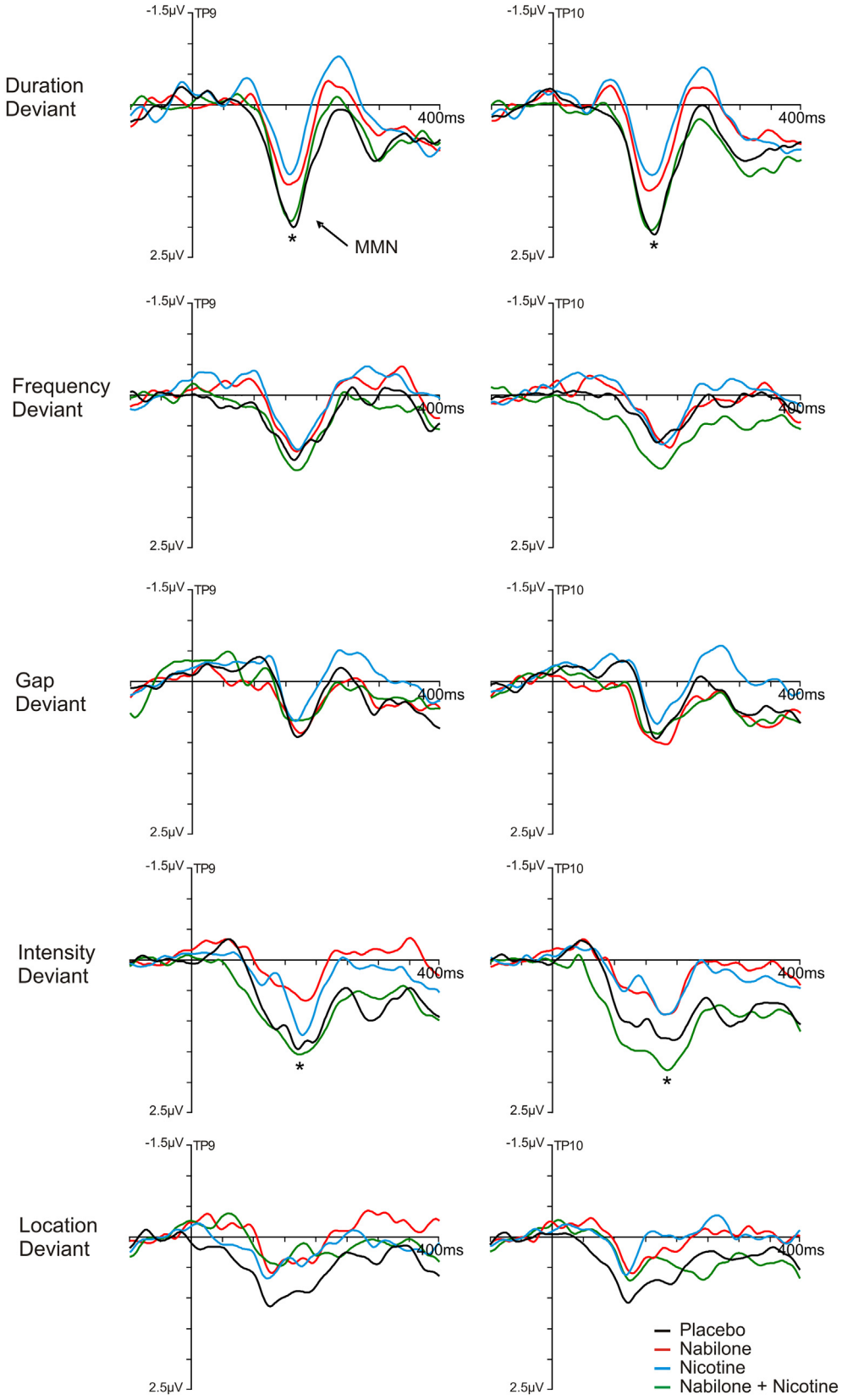

Fig. 5. Grand averaged difference MMN waveforms recorded at left (TP9) and right (TP10) temporal (mastoid) scalp sites for each deviant and each treatment session. * $p < .05$.

condition (M = 1.80 μV, S.E. ± 0.18) was significantly (p = .01) greater than in the nabilone condition (M = 1.21 μV, S.E. ± 0.19). MMN in the combination (M = 2.05 μV, S.E. ± 0.38) treatment was also significantly greater than MMN in the nabilone (p = .04). Placebo treatment MMN was not significantly different from the nicotine treatment MMN (M = 1.49 μV, S.E. ± 0.22), which was also similar to MMN in the nabilone and combination treatments.

3.2.5. Location deviant

Significant treatment [$F(3,57) = 0.84$, $p > .05$], electrode site [$F(1,19) = 0.15$, $p > .05$] or treatment x electrode interaction effects [$F(3,57) = 1.09$, $p > .05$] were not observed for the location deviant, which produced MMN amplitudes across temporal sites that were the same for placebo (M = 1.31 μV, S.E. ± 0.31), nabilone (M = 0.95 μV, S.E. ± 0.17), nicotine (M = 0.97 μV, S.E. ± 0.21), and combined treatment (M = 0.82 μV, S.E. ± 0.19) conditions.

3.3. Adverse events

Treatment differences were not observed with either physical or psychological symptoms.

4. Discussion

This is the first human study to examine both the separate and combined effects of a nAChR and CB_1R agonist on early auditory information processing, using a multi-feature paradigm to assess their modulating effects on MMN generation in response to detection of auditory intensity, frequency, duration, gap, and location deviants. Depending on cortical region and deviant type, separate activation of nicotinic and cannabinoid receptors with nicotine and nabilone, respectively, impaired auditory deviance detection as evidenced by MMN amplitude attenuation. Evidenced by increases in MMN amplitudes, combined activation of these receptors with co-administration of nicotine and nabilone enhanced deviance detection and prevented detection impairment associated with separate activation of these receptors. The present study findings contribute to our understanding of the role of nAChR- and CB_1R- dependent neurotransmission on MMN generation.

Nicotinic modulation of MMN was observed only during duration deviance detection, whereby duration MMN recorded at temporal regions during nicotine treatment was shown to be reduced compared to placebo treatment, an effect found only at mastoid recording sites. As far as we are aware, this is the only study that has examined and reported on nicotinic influences on temporal MMNs elicited by duration deviants. In a previous study with healthy humans, frontal duration MMN was also reduced by nicotine (Dunbar et al., 2007), but individual differences in nicotine effects on frontal MMNs have also been reported, with individuals who display relatively large MMN amplitudes exhibiting MMN reductions with nicotine, while those who display relatively small amplitudes, evidencing MMN amplitude increments with acute nicotine (Baldeweg et al., 2016; Martin et al., 2009). Nicotine is a non-selective nAChR agonist and its modulating effect on MMN may be due to activation of one or more nAChR subreceptors. However, selective activation of the α7 nAChR subunit with citicoline has also been shown to increase frontal duration MMN in small amplitude individuals and to reduce duration MMN in individuals with large amplitudes (Knott et al., 2015).

Cannabinoid receptor activation exerted a similar and additional modulating effect as nicotinic stimulation on auditory deviance detection, with nabilone (vs. placebo) treatment acting to diminish MMN generation at mastoid recording sites during both duration and intensity deviance detection. Although cannabis has not previously been investigated with respect to intensity deviants, frontal MMN generation in response to duration deviants has been diminished by acute treatment with the CB_1R agonist rimonabant but only when co-administered with the NMDA receptor agonist ketamine (Roser et al., 2011), and unlike the reduction seen with frontal pitch MMNs, frontal duration MMN was generally unaffected by chronic cannabis use (Roser et al., 2010), except in heavy long-term users, who evidenced reduced frontal and central scalp duration MMNs compared to light short-term users (Impey et al., 2015). Although studies have differed with respect to MMN recording regions and auditory deviance features, there is some similarity between our present MMN findings and MMN effects resulting from chronic exposure to cannabis (i.e., both evidencing MMN attenuation). However, direct comparisons are not easily made as cannabis contains not only the CB_1R agonist THC but other active ingredients including CBD, which has been shown to increase pitch MMNs (i.e., increase auditory discriminability) at central recording sites (Juckel et al., 2007) and has also been suggested to attenuate THC's detrimental effects, including psychotogenic and deleterious cognitive actions (Hahn, 2018).

The separate effects of nicotine and nabilone were limited to MMNs elicited by duration and intensity deviants. Both agonists acted to reduce detection of duration deviant changes as evidenced by attenuated MMN amplitudes (vs. placebo) at mastoid recording sites, suggesting that nicotine and nabilone share common actions either at cortical generators eliciting the temporal MMNs and/or NMDAR activity modulating these generators. For deviants not exhibiting MMN influences either by nicotine or nabilone, doses may not have been sufficient to activate nAChRs/CB_1Rs or perhaps individual variability in response to agonist treatment may have prevented significant treatment effects. Taking note of previous work documenting an 'inverted-U' shaped pattern with nicotine/nAChR agonist treatment (Knott et al., 2014, 2015; Smith et al., 2015), future research may benefit by targeting these individual differences, examining nicotine/nabilone response in relation to baseline MMN amplitude.

Of particular interest with these present study findings is the observation that separate nabilone and nicotine effects on MMN-indexed auditory deviance detection were limited to mastoid recording sites, proximate to temporal cortex, and were not found with MMN recordings over frontal cortex. Shown with pitch MMNs, an earlier report of amplitude enhancement with cannabis extract at central but not frontal cortical regions suggested that cannabis may mainly affect the temporal generators of MMN in the primary auditory cortex (Roser et al., 2010). Together, EEG and magnetoencephalography (MEG) studies suggest that both the temporal and frontal cortices contribute to MMN generation and whereas attenuated responses of the frontal MMN may reflect a dampened attention-switching function, a deficient temporal MMN is more likely associated with auditory perception and discrimination impairments.

It is important to note that while nicotine impaired mastoid-derived duration MMN, nabilone attenuated both duration and intensity MMNs. With respect to the duration deviant, the processing of duration is thought to occur at lower levels as a contiguous series of short duration epochs which are subsequently recompiled in the auditory cortex (He, 1998). Accordingly, stimulus duration encoding, a form of temporal processing, may involve more complex processing in the auditory cortex compared to other acoustic features, perhaps making the process more vulnerable to nAChR and CB_1R insults or to competing (resource-draining) auditory stimulation including AVHs. This suggestion, however, is out of line with evidence that a previous investigation, using the same nicotine dose as our study, found enhanced automatic temporal processing as measured by MMN (Martin et al., 2009). Another possibility stems from the observation that acoustic energy sums over time, producing loudness increment with longer tones, as opposed to short tones (Scharf, 1978), raising the possibility that the observed impairment seen with nicotine and nabilone stems from reduced sensitivity to perceived loudness cues. When considered in the context of longer tones producing perceived loudness increments, it is possible that the MMN impairment seen with duration and intensity deviants are related and is more impacted by cannabinoid than nicotinic transmission.

At temporal regions, combination treatment acted to block the deviance detection impairments induced with separate administration of nabilone (duration and intensity MMNs) and nicotine (duration MMN), negating the attenuation in deviance detection so that it was comparable to that assessed during placebo. Additionally, although not producing MMNs different from those observed during placebo, combination treatment significantly increased MMNs above MMN amplitudes generated during nabilone (duration and intensity MMNs) and nicotine (duration MMN) treatments administered separately. These later observations suggest that, beyond exerting mutual antagonist effects, nabilone and nicotine combined may enhance neuronal mechanisms underlying MMN generation in response to the automatic detection of specific auditory features. Clearer evidence for the enhancing properties of combined nabilone and nicotine treatment is shown at frontal recording regions where MMN amplitude during location deviance detection was not affected by either nabilone or nicotine treatment but was significantly increased by combined treatment compared to placebo.

Understanding these regional differences in response to pharmacological treatments is limited by our knowledge of source generating MMNs. With MMN displaying its largest amplitude over fronto-central regions and an inverted polarity over mastoids, this scalp distribution has been explained by two sources; a source in and around the auditory cortex in the temporal lobe (thus the inversion at sites inferior to the auditory cortex) and also, a contribution from the frontal lobes (Näätänen et al., 2007). Activity recorded at the mastoid indexes the temporal MMN subcomponent and is believed to reflect the actual detection of change. Both the temporal and frontal sources contribute to the activity recorded at frontal scalp sites, with the frontal MMN subcomponent likely representing a call for further evaluation of the deviant event, perhaps involving attention-switching to the deviance. Dissociation of these cortical regions in MMN responsivity to nicotine/nabilone treatments, which also has been observed in response to different task demands (Muller-Gass et al., 2005), may in part reflect differences in the number or sensitivity of nicotinic and cannabinoid receptors in these cortical areas, which have also evidenced abnormal expression of these receptor systems in schizophrenia. Caution should be heeded in interpreting these scalp distribution differences. Dissociating frontal and temporal contributions to the MMN and its response to nicotine/nabilone in future work might be best accomplished by source dipole analysis.

To date, the neural mechanisms underlying acute pharmacodynamics responses to CB_1R and nAChR agonists are not entirely clear. Mainly dependent on glutamatergic NMDA receptor functioning, the MMN is reduced in healthy humans with NMDA receptor antagonists such as ketamine (Näätänen and Kahkonen, 2009). Nabilone and nicotine act as modulators of postsynaptic neurotransmitter release via activation of presynaptic CB1Rs and nAChRs, respectively. Possibly accounting for the reduction in MMN generation seen with nabilone, limited research in humans support the evidence that cannabis use reduces levels of glutamate-derived metabolites in both cortical and subcortical brain areas, and preclinical research consistently suggests that THC depresses glutamate synaptic transmission via CB1R activation, affecting glutamate release and disrupting synaptic plasticity (Colizzi et al., 2016). Dysregulation of plasticity is in part related to aberrant neuromodulatory systems (e.g. acetylcholine, dopamine) that affect plasticity by increasing neuronal excitability and signal to noise ratio (Voss et al., 2019). Nicotine also increases glutamate release, neurotransmission and synaptic plasticity by activating nAChRs, particularly those containing the α7 subunit, which are often co-localized with NMDA receptors on nerve endings (Koukouli and Masko, 2015). In the rat auditory cortex, α7 nAChRs have been shown to stimulate glutamate release and selectively potentiate NMDA receptor-mediated synaptic transmission (Aramakis and Metherate, 1998). These nicotine effects on glutamate activity however occur relatively quickly, are of short duration and are observed with low agonist concentrations, and high agonist doses and prolonged exposure typically desensitize α7 nAChR (Koukouli and Masko, 2015). Although temporal patterns of nAChR response to smoke-inhaled nicotine or oral nicotine in humans are not entirely clear, desensitization effects are not manifested at all behavioural and physiological parameters (Thomsen et al., 2010), α7 nAChR desensitizes very quickly (vs. α4β2 subunit) in response to high agonist concentrations both in vitro (Dani et al., 2000) and in vivo (Marks et al., 2002). In our present study, continuous exposure to our oral nicotine dose (6 mg), previously shown to produce blood nicotine levels equivalent to that of a medium nicotine-yield cigarette, may have resulted in nicotine acting as a functional antagonist by desensitizing α7 nAChRs and thereby reducing glutamate release and diminishing MMN generation. Although this suggestion remains to be assessed in future dose-response studies, acute treatment with the choline supplement citicoline, which possesses α7 nAChR agonist properties, most often produced MMN amplitude increases with relatively lower (500 mg) than high (1000 mg) oral doses in healthy participants (Knott et al., 2015).

Relative to the dampening effects on sensory processing induced with separate administration of nabilone and nicotine, combined administration of these two agonists produced no additive or synergistic effects but resulted in blocking the diminishing effects exerted by nabilone (mastoid derived duration and intensity MMN) and nicotine (mastoid derived duration MMN) or producing an opposing response of enhanced auditory discriminability as evident with increases in frontal-derived location MMN amplitude. One may reasonably speculate that this enhancement likely involved neuromodulation of neurotransmitters other than glutamatergic systems, as human studies combining drugs that enhance (nicotine) and diminish (ketamine) glutamate neurotransmission have evidenced no increases or decreases in MMN generation (Hamilton et al., 2018; Knott et al., 2012; Mathalon et al., 2014). In addition to regulating cholinergic neurotransmission, these two neuromodulators, nabilone and nicotine, affect release in multiple neurotransmitter systems (e.g. dopamine, serotonin, GABA). Pharmacological investigations inducing changes in the individual neurotransmitter systems however have resulted in mixed effects on MMN generation and cannot reasonably account for MMN enhancement seen with our combination treatment (Rosburg et al., 2004), although studies examining combined pharmacological agonist and antagonist actions within each of these systems has yet to be conducted. Furthermore, how nAChR and CB_1R systems, separately and together, act to modulate the complex interactions between different neurotransmitters (dopamine, serotonin, GABA) and endogenous cannabinoids to moderate sensory/cognitive processing is still unknown and requires addressing. Biochemical, physiological and behavioural evidence support a functional interaction between nicotine and cannabinoids and, although there are areas where they exert contrasting effects (e.g. cognition and food intake), certain animal and human studies suggest that reinforcing effects are likely to be enhanced by joint use (Viveros et al., 2006). Further studies investigating co-treatment with nicotinic and cannabinoidergic agents are needed to understand potential benefits on sensory processing and the role of these interacting systems on sensory processing impairments.

5. Limitations

This present study has a number of strengths including a double-blind, placebo controlled design, randomized treatment with separate and combined drugs, use of a multi-feature paradigm, and analysis of MMN generation at frontal and temporal regions. There are also several study weaknesses which temper the significance and interpretation of our findings. Overnight abstinence from alcohol/substances prior to test days was only verified verbally and participants were not subjected to urine analysis on the testing days to determine recent exposure. Drugs were administered at one dose level, and additional work examining dose-response and time-response effects is needed. This is particularly

the case for nicotine as low and high doses can activate and desensitize nAChRs, respectively. Nicotine is a non-selective nAChR agonist and the present findings cannot be directly linked to the pharmacodynamics of any specific receptor subtype. Nabilone was administered at the lowest available clinical dose so as to be able to assess the pharmacodynamics (MMN) response independent of psychotic symptoms which would have accompanied higher doses. Both nicotine and nabilone were administered orally and these effects cannot be easily compared to smoked cannabis or tobacco, which contain other centrally active constituents. Single dose effects do not necessarily parallel effects seen with chronic treatment and studies investigating repeated dosing over time are required. Deviance detection was assessed electrophysiologically with scalp recorded ERPs which do not fully capture all cortical activity mediating sensory processing and in future studies this can be combined with neuroimaging approaches to assemble a more complete neural profile of nicotine and cannabinoid actions in the human brain. Finally, although the use of healthy volunteers may have provided a clearer picture of drug effects that is not possible with individuals diagnosed with schizophrenia, these types of brain-based, pharmacological studies investigating separate and combined nicotinic and cannabinoid treatments need to be conducted in patients in order to understand the mechanisms underlying excessive co-use of tobacco and cannabis in this disorder.

6. Relevance to schizophrenia

Observations of separate and combined effects of nAChR and CB_1R agonists on auditory sensory processing have potential clinical implications for patients diagnosed with schizophrenia (SZ). Viewed as a reflection of self-medication (Khantzian, 1997) or as an involuntary, general addiction vulnerability (Chambers, 2009), substance use disorder prevalence is high in SZ (Regier et al., 1990; Swofford et al., 2000) as is reflected by increased rates of tobacco (de Leon and Diaz, 2005; Winterer, 2010), cannabis (Green et al., 2005; Koskinen et al., 2010), and their combined use (Rabin et al., 2014; Rabin et al., 2011). Compared to the normal population, extensive perturbations in nAChR (Olincy and Freedman, 2012), CB_1R (D'Souza et al., 2009), and NMDA receptor function (Javitt, 2012) in SZ together with consistent evidence of auditory sensory dysfunction (Javitt and Sweet, 2015) and robust deficits in auditory deviance detection (Näätänen and Kahkonen, 2009) has in part propelled studies on the effects of tobacco/nicotine (e.g. Dulude et al., 2010; Fisher et al., 2012; Inami and Kirino, 2019) and cannabis (e.g. Pesa et al., 2012; Rentzsh et al., 2011; Roser et al., 2019) on auditory MMN generation in SZ. Given the strong correlation between MMN deficits and impaired cognitive and functional outcome in SZ (Näätänen and Kahkonen, 2009), preliminary findings from these latter MMN studies showing enhanced deviance detection with acute nicotine and chronic cannabis use in SZ support additional investigations aimed at the potential modulatory actions of combined nAChR and CB_1R agonist treatment on aberrant MMN generation in SZ patients.

7. Conclusions

Heavy smoking of tobacco and cannabis is evident in people with schizophrenia, and studies investigating the separate and combined role of nicotinic and endocannabinoid systems in relation to clinical and sensory/cognitive symptoms are needed to understand the neurobiological mechanisms underlying separate and simultaneous use of these substances in this disorder. In this study on auditory sensory processing in healthy volunteers, deviance detection, as assessed with MMN, was examined in response to a single dose of nicotine and nabilone and, depending on acoustic deviant feature, showed impairment at temporal cortex with each separate treatment and was enhanced at frontal cortex with combined treatment. Although the specific neural mechanisms responsible for these effects are not clear, the findings have implications for auditory sensory dysfunction in schizophrenia and its potential targeting with nicotinic-cannabinoidergic treatments.

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