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Mismatch negativity in tobacco-naïve cannabis users and its alteration with acute nicotine administration☆

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ABSTRACT

Chronic cannabis use may interact with factors, such as age of onset of cannabis use, family history, and genetic factors, to elicit schizophrenia (SZ)-like symptoms, including sensory and cognitive deficits. However, evidence of a relationship between cannabis use and cognitive impairment is confounded by concomitant use of tobacco. The objective of this study was to compare tobacco-naïve cannabis users with individuals without a history of tobacco/cannabis use on the auditory mismatch negativity (MMN) event-related potential (ERP), a neural measure of auditory deviance detection which is diminished in SZ. An exploratory arm of the study, conducted within a randomized, double-blind, placebo controlled design, examined the acute effects of nicotine gum (6 mg) on MMN in cannabis users. MMN was recorded in response to 5 deviant stimuli within an optimal MMN paradigm in 44 healthy, non-tobacco smoking volunteers aged 18–26. Cannabis users ($n = 21$) started smoking cannabis prior to age 17, at least 1 joint per month. To examine the effects of chronicity, users were grouped into relatively heavy long-term (HLT; $n = 11$) users and light short-term (LST; $n = 10$) users. Impaired deviance detection was shown in cannabis users vs. nonusers as reflected by a smaller MMN to duration deviants. Chronicity of use was also associated with MMN alterations, as HLTs displayed a reduced duration and gap MMN vs. LSTs. Compared with placebo, nicotine treatment enhanced select MMN deviants in cannabis user subgroups. As deficits associated with early and persistent cannabis use are similar to those seen in SZ, these dose-dependant disturbances in early sensory processing with cannabis use may be one cognitive pathway which mediates an increased risk for SZ in vulnerable youth, and be influenced by concurrent cigarette smoking behavior.

1. Introduction

Cognitive impairment, characterized by deficits in perception, attention and working memory, has been proposed to be the core feature of schizophrenia (SZ) as studies have shown that cognitive deficits are directly correlated with negative symptoms and functional outcome, as well as being a target for pharmacological treatment (Elvevag and Goldberg, 2000; Green, 1996; Green et al., 2000). These cognitive deficits may be confounded by comorbid drug use and cannabis use in particular, with many SZ patients having dual diagnosis with cannabis abuse (Margolese et al., 2004) and an estimated 20–50% of patients meeting criteria for lifetime use (Arseneault et al., 2002). *Cannabis sativa* is the most frequently used illicit drug in the world, with Δ9-tetrahydrocannabinol (THC) being identified as the major psychoactive constituent (Gaoni and Mechoulam, 1964). The activity of THC is mediated by agonistic effects at the central cannabinoid (CB1) receptor (Matsuda et al., 1990), with the highest density of CB1 receptors found in the cerebral cortex, basal ganglia, hippocampus, anterior cingulate cortex and cerebellum; brain regions which are important in cognitive processes such as attention, memory and executive functions and are critically involved in the pathogenesis of SZ spectrum disorders (Dean et al., 2001; Herkenham et al., 1990). Increasing evidence suggests that early and heavy cannabis exposure may increase the risk of developing psychosis and that cannabis exposure may be a "component cause" that interacts with other factors such as genetic vulnerability (Sewell et al., 2010; Arseneault et al., 2002).

A number of studies and lines of evidence support a close relationship between cannabis use, the endogenous cannabinoid system (eCB) and SZ (Leweke et al., 2004; Solowij and Michie, 2007; Sewell et al., 2010). First, both acute and chronic THC have been shown to induce not only memory impairments, similar to those seen in SZ including

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working memory, episodic memory encoding, impaired retrieval, but also attentional deficits and impaired executive functions (Fletcher and Honey, 2006; Skosnik et al., 2001). These impairments have been observed beyond acute intoxication (Solowij, 1998) and clinical signs of chronic cannabis use may resemble negative symptoms, also known as amotivational syndrome (Schwartz et al., 1989). Second, THC exposure in SZ patients has been found to exacerbate clinical symptomatology (D'Souza et al., 2005). Cannabis consumption in patients has been found to worsen positive symptoms (Turner and Tsuang, 1990; Weil, 1970) and results in a poor response to neuroleptic medications (Bowers et al., 1990), poorer treatment compliance, enhanced hospitalizations and liability to relapse (Hall and Degenhardt, 2000; Martinez-Arevalo et al., 1994; Linszen and van Amelsvoort, 2007). Third, several epidemiological studies have shown that cannabis use can increase the risk for the development of schizophrenia (Andreasson et al., 1987; Arseneault et al., 2002; van Os et al., 2002). This is a dose-dependent relationship whereby people who have used cannabis frequently are at increased risk of psychotic outcomes, as well as the development of schizophrenia-like cognitive dysfunction (Henquet et al., 2005; LeVeke and Koethe, 2008; Radhakrishnan et al., 2014). This association is particularly seen with heavy cannabis use prior to the age of 17 when the brain is still developing, which increases the likelihood of developing schizophrenia later on in life (Fernandez-Espejo et al., 2009; Sundram, 2006). Finally, there is also evidence suggesting that there are eCB alterations in SZ. Post-mortem studies have reported an increased density of CB1 receptors in the dorsolateral prefrontal cortex (Dean et al., 2001) and anterior cingulate (Zavitsanou et al., 2004) and endocannabinoid levels in cerebrospinal fluid of SZ patients were found to be twofold higher in comparison to healthy controls (Leweke et al., 1999).

The cognitive deficits associated with SZ and cannabis use can be assessed using non-invasive event-related potentials (ERPs), which are derived from scalp electroencephalographic (EEG) recordings and reflect the brain's response to discrete stimuli. The high temporal resolution of ERPs (milliseconds) allows for the investigation of early stimulus processing through to higher-order cognitive operations (Light et al., 2010), several of which are notably impaired in SZ patients (Braff and Light, 2004). In patients, these objectives, brain-based measures have been related to clinical symptoms (Fisher et al., 2008, 2010), neurocognitive deficits (Javitt, 2000) and real-world functioning (Light and Braff, 2005). The auditory mismatch negativity (MMN) is a pre-attentive ERP component elicited by any discriminable change of a repetitive sound (Näätänen, 1995) and is discerned as a negative peak maximal at frontal sites, and occurring with a latency of 90–250 ms after an auditory stimulus that deviates in any acoustic dimension (including frequency or duration) from a sequence of standard auditory stimuli (Näätänen and Ahlo, 1997). The MMN is automatically generated in response to a low-probability (rare) novel/deviant stimulus, which is compared with a well-formed sensory or "echoic" memory trace of the standard, repetitive auditory stimulus. The MMN will be elicited in response to violations of the automatically formed memory trace of acoustic (or visual) regularities. Thus, deviance detection indexed by MMN is thought to reflect sensory memory processes, representing a neural marker of human "echoic" memory, an early form of memory representation of auditory stimuli (Näätänen and Alho, 1995).

Deficits in MMN generation are a robust feature in chronic SZ (Näätänen and Kähkönen, 2009; Shelley et al., 1991; Javitt et al., 1993; Umbricht and Krljes, 2005; Youn et al., 2003), which are especially evident with duration deviants (Michie, 2001), however MMN reduction in schizophrenia has been reported with frequency (Javitt et al., 1993; Hirayasu et al., 1998; Todd et al., 2008), intensity (Fisher et al., 2008; Todd et al., 2008) and perceived location (Alain et al., 2002) deviants as well. MMN deficits have been significantly correlated with negative symptoms (Hirayasu et al., 1998; Javitt et al., 2000; Kasai et al., 2002), positive symptoms and hallucination severity (Fisher et al., 2011a), duration of illness (Umbricht and Krljes, 2005) and functional outcome status in schizophrenia (Kawakubo et al., 2007).

In a recent study, to assess the possible similarities between SZ and cannabis use in terms of sensory memory function, Roser et al. (2010) tested the hypothesis that heavy cannabis use in healthy volunteers is associated with a deficit in MMN generation. Long-term and chronic cannabis abusers, defined as those having smoked at least 15 joints per week for at least 8 years, exhibited reduced frequency MMN amplitudes compared to non-users at central recording sites, and short-term and light cannabis users at frontal sites. A study by Rentzsch et al. (2011) also investigated MMN in heavy cannabis users, who reported daily cannabis use for an average of 8 years, compared to non-users, as well as SZ patients, both users and non-users. Significant differences were observed among groups with frequency MMN (but not duration MMN) at frontal sites, with cannabis users displaying attenuated amplitudes compared to non-users. Interestingly, SZ cannabis users did not differ from healthy control cannabis user deficits (Rentzsch et al., 2011). However, both studies included tobacco smokers and nicotine, the main psychoactive component of tobacco, is known to have cognitive enhancing properties (Rezvani and Levin, 2003; Heishman et al., 1994) and has been found in some, but not all studies to enhance MMN in both healthy controls (Harkrider and Hedrick, 2005; Inami et al., 2005; Fisher et al., 2010), particularly in individuals with low MMN amplitudes (Knott et al., 2014), and SZ patients (Dulude et al., 2010; Inami et al., 2007). In the Roser study (2010), after controlling for the increased nicotine use in cannabis users, differences between cannabis users and healthy controls were no longer significant. Also, participants were only required to abstain from smoking cannabis 24 h prior to testing. Because THC accumulates in body fat and is slowly excreted and persists in the urine of chronic users up to several weeks (Johansson and Halldin, 1989), these findings may have been confounded by residual levels of cannabis, representing acute vs. long-term effects in the brain. With respect to drug interactions, adolescent exposure to nicotine has been found to modify acute functional response to cannabinoid agonists in rats (Viveros et al., 2006) and chronic nicotine use has been shown to mask disruptions in cognitive neurocircuitry associated with adolescent cannabis use (Jacobsen et al., 2007). Cannabidol, a non-psychoactive ingredient of the cannabis plant has been shown to inhibit the function of the α7 nicotinic acetylcholine receptor (Mahgoub et al., 2013), which is diminished in numbers in SZ (Freedman et al., 2000) and when stimulated with a selective agonist has resulted in increased sensory memory in healthy individuals with low MMN amplitudes (Knott et al., 2015).

1.1. Objectives and hypothesis

Given the close relationship between cannabis use, the eCB system, and SZ, it is possible that early and persistent use of this drug may negatively influence cognition including sensory processing which, when combined with other risk factors, may predispose vulnerable individuals to SZ. While chronic cannabis use has been shown to result in selective auditory processing impairments similar to those seen in schizophrenia (Roser et al., 2010; Rentzsch et al., 2011), methodological issues surrounding the potential influence of tobacco use history may have influenced these results. To better understand the effects of long-term cannabis exposure independent of tobacco use, the primary objective of this study was to investigate MMN-indexed auditory deviance detection in abstinent chronic cannabis users with no history of cigarette smoking. As MMN attenuation in SZ has been associated with a number of deviant acoustical features and to vary with scalp region, an "optimal" MMN paradigm, which allows for MMN to be elicited by 5 sound deviants (Näätänen et al., 2004), was administered and assessed at frontal and central recording sites. It was hypothesized that cannabis users (vs. non-users) would exhibit impaired auditory deviance processing as indexed by reduced frontal and central MMN amplitudes compared to non-users. Second, as epidemiological studies in

the general population have repeatedly found that cannabis use increases the risk of developing a psychiatric disorder in a dose-dependant manner (Arseneault et al., 2002), it was predicted that greater MMN deficits would be associated with increased cannabis exposure. Confirmation of these hypotheses was expected primarily with respect to duration and frequency MMNs, which are consistently diminished in SZ.

As information on the direct effects of nicotine in cannabis users would be informative with respect to nicotinic-cannabinoid system interactions, an exploratory arm of this study examined the acute effects of nicotine administration in our sample of users and assessed how these effects varied with chronicity of cannabis use.

2. Method

2.1. Participants

A total of 44 right-handed (assessed with the Edinburgh Handedness Inventory; Oldfield, 1971), non-cigarette smoking male volunteers (21 cannabis users, 23 non-users) between the ages of 18–26 years ($M = 20.13$ years, $SD \pm 2.33$) were recruited from the local community and were mostly composed of undergraduate students. For study entry, cannabis users had to be smoking cannabis prior to the age of 17, smoking at least 1 joint per month from the beginning of cannabis use, and at least 1 joint per week for the past month prior to testing. Non-cannabis users had to have smoked less than 10 joints in their lifetime and none in the past year. In addition to having normal hearing, all participants were required to be non-cigarette smokers, having consumed no more than 100 cigarettes in their lifetime, or equivalent tobacco products, and none in the past year. Non-smoking status was verified by an analysis of their expired air carbon monoxide level (CO), which was required to be below 3 parts per million (ppm). At screening participants were subjected to urine toxicology screening to test for THC presence. Fifteen of the 21 cannabis users tested positive while none of the non-users tested THC positive. Exclusion criteria included current medication use, current or past psychiatric history (as assessed by the Structured Clinical Interview for DSM-IV Non-Patient Edition [SCID-NP; First et al., 1995]) or family history of SZ in first degree biological relatives (as assessed by the Family Interview for Genetic Studies [FIGS, 1991]), treatment for substance abuse, and any neurological (seizures, recent [<6 months] head trauma with loss of consciousness) or major medical illnesses. None of the cannabis users met DSM-IV diagnostic criteria for cannabis abuse disorder. Prior to testing, all participants signed an informed consent form and were compensated ($25 CAD per session) at the completion of the study. The study was approved by the Research Ethics Boards of the Royal Ottawa Health Care Group and the University of Ottawa.

2.2. Design

Non-users attended the lab for 1 test session while the cannabis users were assessed in two sessions separated by a minimum 1 day interval. For the users, MMNs were assessed within a randomized, double-blind, placebo controlled design, with assessments being conducted under acute nicotine and placebo treatment. For half of the users, nicotine was administered in the first session and placebo in the second session, while the remaining half received treatments in the reverse order.

2.3. Procedure

Testing sessions were held in the morning between 8:00 a.m.–12:30 p.m. following overnight abstinence from drugs, alcohol, and medication and 2 h of pre-session abstinence from caffeine. Cannabis users were also required to abstain from smoking cannabis for a minimum of 10 days prior to their testing session ($M = 14$ days, $SE \pm 3$, range 11–23 days). Urine screens were used to verify the presence or absence of THC at the test sessions. Although this 10 day abstinence period does not allow for participants to be completely free of THC, it helps reduce any acute effects of residual THC on study measures. The urine tests for all non-users were negative at their tests session. All of the 6 users who tested negative during their initial study screening tested negative for both of their test sessions. Of the 15 users who tested THC positive during their initial study screen, 6 were positive in both test sessions, 4 were negative in each test session, and 3 were positive in their first session but negative in their second session. Upon arrival at the laboratory and following urine screens, participants were escorted to a sound attenuated, electrically shielded testing chamber for EEG hook-up and then MMN assessment was initiated. During electrode hook-up, cannabis users were administered their placebo or nicotine treatment.

2.4. Nicotine

Nicotine (6 mg) was administered orally as two pieces (2-mg Nicorette and 4-mg Nicorette Plus) of cinnamon-flavored polacrix gum. The placebo consisted of 2 pieces of commercially available cinnamon flavored gum, which matched the active nicotine gum pieces in size and texture. Participants were blindfolded and required to wear a nose plug throughout administration to reduce any sensory differences between placebo and nicotine gums. Nicotine gum was chewed for a total of 25 min according to manufacturer's guidelines, which required participants to bite twice per minute (as cued by an auditory tape recording) and to "park" gum between teeth and cheek between bites. After the gum was removed, participants chewed a commercially available mint flavored "wash out" gum for 2 min to mask any residual flavor differences. On the basis of previous pharmacokinetic studies, blood nicotine level was expected to peak at 30 min and to be between 16 and 26 ng/ml (elimination half-life of approximately 2 h), which is comparable to the 15–30 ng/ml level typically seen with smoking of a single cigarette with medium nicotine yield (Hukkanen, Jacob, & Benowitz, 2005).

2.5. Stimuli

Participants were presented binaural auditory stimuli through headphones while viewing a silent video (The Blue Planet by BBC). In the multi-feature MMN paradigm (Näätänen et al., 2004), the standard stimuli were tones of 75 ms duration (including 5 ms rise and fall) composed of three sinusoidal partials of 500, 1000, and 1500 Hz. The deviant tones differed from the standard tones in frequency, duration, intensity, perceived location of sound origin or contained a gap in the middle of the tone. Except where stated, the deviants were identical to the standards. Presented binaurally through headphones, all stimuli (with the exception of the intensity deviants) were at a sound pressure level (SPL) of 70 dB with equal phase intensity in each channel. Half of the frequency deviants were 10% higher (composed of 550, 1100, and 1650 Hz partials) while the other half were 10% lower (450, 900, and 1350 Hz partials). Half of the intensity deviants were at 60 dB while the other half were at 80 dB. The perceived difference between the standard tone and the location deviant was approximately 90°; the change in perceived location of sound origin was obtained by creating a time difference of 800 μs for half of the location deviants to the right channel and half of the deviants to the left. The duration deviant was only 25 ms, while the gap deviant was created by removing 7 ms (including 1 ms rise and fall) from the middle of the standard stimulus. In each sequence, the first 15 tones were standards, followed by a sequence whereby every second tone was a standard ($P = 0.5$) and every other one was one of the five deviants ($P = 0.1$ each). The deviants were presented so that each deviant category was presented once every 5 deviants and 2 deviants of the same category were never presented consecutively. The stimulus onset asynchrony (SOA) was 300 ms, and the

stimuli were presented in 3 sequences of 5 min each (1845 stimuli) for a total of 15 min (5535 stimuli).

2.6. Recordings

ERPs were recorded with Ag/Ag Cl electrodes placed on 8 scalp sites including Fz, F_4, F_3, Cz, C_4, and C_3. A mid-forehead site served as ground and an electrode on the nose served as a reference. Additional electrodes were placed on orbital sites for bipolar recordings of vertical (VEOG) and horizontal (HEOG) electro-oculographic activity. Electrical recordings were carried out using a Brain Vision V-8 Amp® (Brain Products GmbH, Munich DE) amplifier and Brain Vision Recorder® (Brain Products GmbH, Munich DE) software. Electrode impedances were kept below 5 kΩ and electrical activity was sampled at 500 Hz, with bandpass filters set at 0.1–100.0 Hz. Off-line analysis was performed using Brain Vision Analyzer® (Brain Products GmbH, Munich DE) software. For each stimulus, electrical epochs of 500 ms duration (beginning 100 ms prior to stimulus onset) were ocular corrected, digitally filtered (0.1–8 Hz), and baseline corrected (relative to the prestimulus segment), and only epochs with EEG voltages below 75 μV were used for final ERP averages, which were constructed separately for each standard and deviant stimulus type. No significant differences in number of rejected epochs were observed across deviant types or between groups. 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 stimulus. As the grand averages indicated some MMN waveforms were below baseline, MMN was measured as the difference between the most negative peak value between 100 and 250 ms and the preceding peak positive trough between 80 and 150 ms. MMN latencies were only measured at Fz, the site of maximal amplitude.

2.7. Questionnaires

The Marijuana Withdrawal Checklist (MWC) listed 22 symptoms of possible cannabis-related mood, behavioral, and physical withdrawal symptoms such as craving, irritability and nervousness. A total withdrawal discomfort score was calculated by summing the rating of each item from a four-point Likert scale (0 = not at all, 1 = mild, 2 = moderate, 3 = severe) and was indicative of the presence or absence of any cannabis withdrawal (Budney et al., 1999).

2.8. Statistics

Analyses were carried out using the Statistical Package for the Social Sciences (SPSS; IBM Corp., Armonk, NY). Comparison of MMNs between non-users was carried out using the data gathered from the users' placebo sessions. MMN amplitudes for each deviant type were subjected to separate two-way mixed analysis of variance (ANOVA) procedures with a between group (2 group: cannabis users vs. non-users) and a within-group factor (6 sites: Fz, F_3, F_4, C_z, C_3, C_4). Analysis of MMN latencies (at Fz) for both groups was similar, but ANOVAs did not contain a site factor. These ANOVAs were repeated with the users who were THC negative at screening being removed from the data set. Results with these secondary ANOVAs were not different from the ANOVAs with the large sample and will not be presented here. In addition, similar 2 × 4 ANOVAs were used to examine the effects of chronicity and intensity of cannabis use, with the cannabis user group being further divided into two subgroups, heavy long-term (HLT; $n = 11$) users and light short-term (LST; $n = 10$) users. These groupings were based on a composite score index which was calculated for each user by multiplying their total number of weeks of cannabis use with their total amount of cannabis consumed per week. The two user subgroups were formed on the basis of a median split of the composite score. Planned comparisons of site × group are reported to fully investigate and localize differences between groups, as done in Roser et al. (2010)'s cannabis study, which observed user vs non-user differences to be limited to central (not frontal) recording regions.

In order to examine nicotine treatment effects in cannabis users, separate repeated measures ANOVA procedures for each deviant type were carried out for group and drug comparisons of MMN amplitudes, each ANOVA containing a between-group factor with 2 levels (HLTs and LSTs) and within-group factors of drug condition with 2 levels (nicotine and placebo) and electrode site with 6 levels (Fz, F3, F4, Cz, C3, C4). MMN latencies (at Fz) were analyzed with similar one-way ANOVAs with no site factor. Separate mixed ANOVAs were conducted with HLT and LST groups and drug factor to evaluate differences in systolic and diastolic blood pressure, heart rate, and WDS and CNRS scores. With all analysis, Greenhouse–Geisser significant ($p < 0.05$) effects were followed up with Bonferroni-adjusted planned comparisons to evaluate study hypothesis.

3. Results

Participant demographics are presented in Table 1. As expected, there were no age differences between cannabis users and non-cannabis users. Based on our stratification method, as expected, HLTs evidenced longer use and greater amount used than LSTs.

3.1. Comparison of users and non-users

3.1.1. Duration deviant

There was a significant main effect of group, $F(1,42) = 3.97$, $p < .05$, which demonstrated that cannabis users ($M = -1.82$ μV, SE ± .25) had significantly reduced duration MMN compared to non-users ($M = -2.52$ μV, SE ± 0.24), shown in Fig. 1. Follow-up planned comparisons of electrode site × group showed that this effect was localized to F_3 ($p < .05$), F_4 ($p < .03$), and C_3 ($p = .07$). With regard to the subgroups of cannabis users, a significant main effect of group, $F(1,19) = 8.42$, $p < .01$, was seen, with heavy long-term users ($M = -1.21$ μV, SE ± .31) displaying reduced duration MMN compared to light short-term users ($M = -2.49$ μV, SE ± .32), shown in Fig. 2. Follow-up planned comparisons showed that this effect was significant ($p < .05$) at all sites.

3.1.2. Gap deviant

Although cannabis users ($M = -1.49$ μV, SE ± .32) displayed reduced MMN compared to non-users ($M = -2.27$ μV, SE ± 0.31) for gap deviants, this effect was not significant ($p = .09$), as shown in Fig. 3. Planned comparisons of group differences by site showed a statistical trend towards reduced MMN amplitudes in users which was localized to F_4 ($p = .08$), Cz ($p = .06$), C_3 ($p = .07$) and C_4 ($p = .08$). With regard to the subgroups of cannabis users, there was a significant main effect of group, $F(1,19) = 16.33$, $p < .001$, with heavy long-term users ($M = -.58$ μV, SE ± .33) displaying reduced gap MMN compared to light short-term users ($M = -2.50$ μV, SE ± .35), as shown in Fig. 4. Follow-up planned comparisons of site × group showed that this effect was significant ($p < .05$) at all sites.

3.1.3. Intensity deviant

There were no significant main differences between cannabis users and non-users (Fig. 5). However, planned comparisons of site × group

Table 1
Summary of demographics for non-cannabis users and cannabis users, with subgroups light short-term users (LST), and heavy long-term users (HLT). Mean values and standard error (SE) are presented.

	Non-users	Cannabis users	HLTs	LSTs
N	23	21	11	10
Age	20.4 ± 2.5	19.8 ± 2.2	20.2 ± 2.5	19.0 ± 1.4
Grams/week	–	3.5 ± 3.4	4.8 ± 4.1	1.9 ± 1.2
Years of use	–	4.3 ± 2.2	5.2 ± 2.6	3.3 ± 1.2

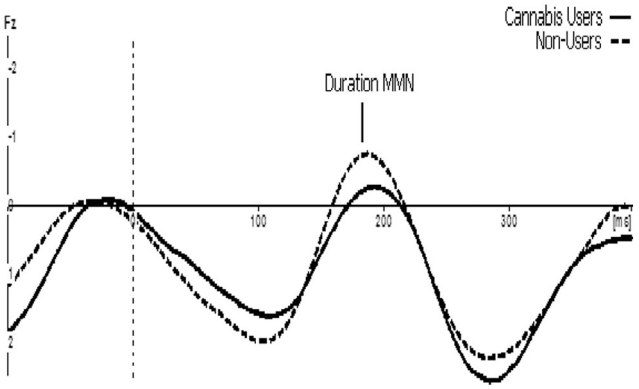

Fig. 1. Grand averaged frontal (Fz) MMN waveforms for cannabis users (solid line) and non-users (dashed line) elicited in response to duration deviants, indicating a significantly reduced ($p < .05$) MMN amplitude in users vs. non-users.

revealed a statistical trend towards reduced intensity MMN amplitudes in users ($M = -1.14$ μV, SE ± .35) compared to non-users ($M = -2.01$ μV, SE ± .33) at Cz ($p = .08$). With regard to the subgroups of cannabis users, although heavy long-term users ($M = -1.26$ μV, SE ± .28) had reduced MMN compared to light short-term users ($M = -1.99$ μV, SE ± .29), this effect was non-significant ($p = .09$) (Fig. 6). Planned comparisons of site × group showed that this trend was localized to Fz ($p = .06$), F3 ($p = .08$) and the differences between HLTs and LSTs became significant at F4 ($p = .05$).

3.1.4. Location deviant

There were no significant main differences between cannabis users and non-users. The subgroup user analysis also did not demonstrate any significant differences between HLTs and LSTs.

3.1.5. Frequency deviant

There were no significant main differences between users and non-users, nor any subgroup differences between HLTs and LSTs.

3.1.6. MMN latency — group effects

With gap deviants, there was a significant difference between groups, $F(1,42) = 4.94$, $p < .03$, with users displaying longer latencies ($M = 122.19$ ms, SE ± 6.09) compared to non-users ($M = 103.48$ ms, SE ± 5.82). There were no significant differences in any other deviant type between users and non-users. There were no significant latency differences between HLTs and LSTs in any deviant type.

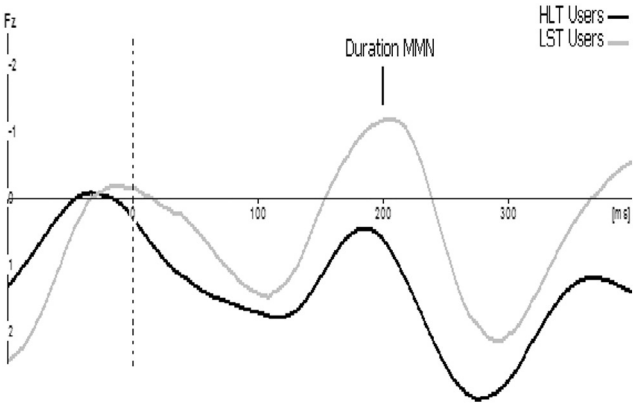

Fig. 2. Grand averaged frontal (Fz) MMN waveforms for HLT (black) and LST (gray) users elicited in response to duration deviants, indicating a significantly reduced ($p < .01$) MMN amplitude in HLTs vs. LSTs.

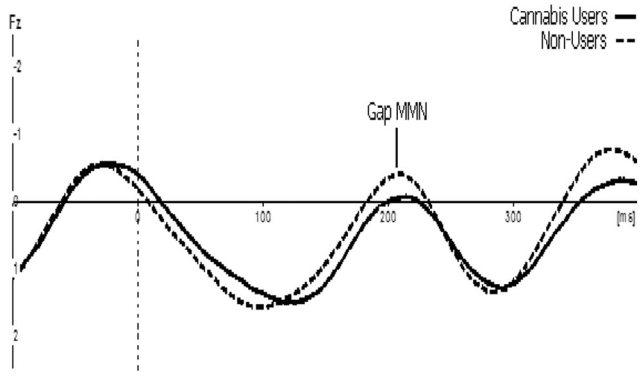

Fig. 3. Grand averaged frontal (Fz) waveforms MMN for cannabis users (solid line) and non-users (dashed line) elicited in response to gap deviants.

3.2. Comparison of nicotine vs placebo in user subgroups

3.2.1. Duration deviant

No main effect of drug or significant drug × group interaction was observed.

3.2.2. Gap deviant

No significant effect of drug or drug × group interaction was observed.

3.2.3. Intensity deviant

There was no significant drug, or drug × group interaction.

3.2.4. Location deviant

There was a main effect of drug, $F(1,18) = 5.04$, $p < .05$, with nicotine ($M = -2.47$ μV, SE ± .43) displaying greater MMN compared to placebo ($M = -1.45$ μV, SE ± .28). There was no significant drug × group interaction.

3.2.5. Frequency deviant

There was no main effect of drug, however, follow-up comparisons of a significant drug × group interaction, $F(1,18) = 8.49$, $p < .01$ demonstrated that in LST users, nicotine ($M = -3.33$ μV, SE ± .59) produced greater, $p < .02$, MMN amplitudes compared to placebo ($M = -1.96$ μV, SE ± .51). Follow-up comparisons also revealed that in the nicotine condition, HLTs ($M = -.928$ μV, SE ± .59) had significantly reduced, $p < .01$, MMN compared to LSTs (M = −3.33 μV, SE ± .59).

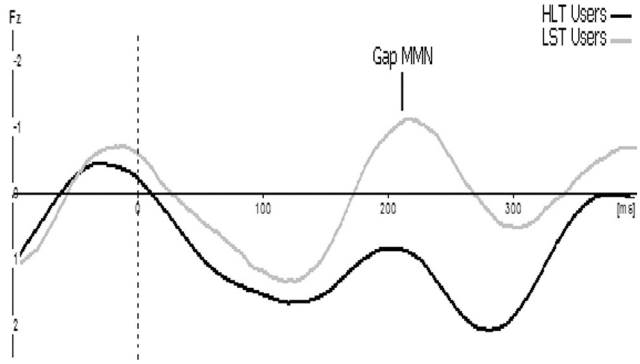

Fig. 4. Grand averaged frontal (Fz) MMN waveforms for HLT (black) and LST (gray) users elicited in response to gap deviants, indicating a significantly reduced ($p < .001$) MMN amplitude in HLTs vs. LSTs.

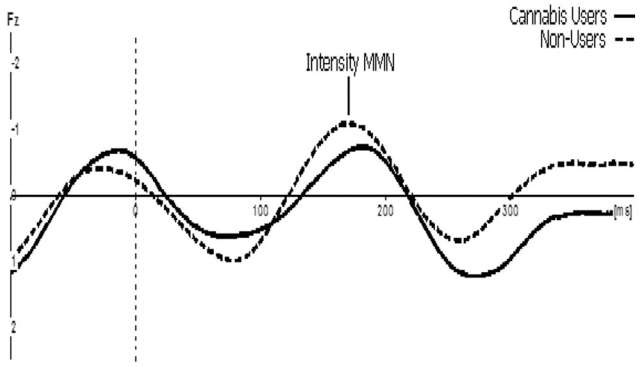

Fig. 5. Grand averaged frontal (Fz) MMN waveforms for cannabis users (solid line) and non-users (dashed line) elicited in response to intensity deviants.

3.2.6. MMN latency—drug effects

There was no main effect of drug or significant drug × group interaction for any deviant type.

3.3. Self-reports

Although users reported some withdrawal symptoms, there was no significant WDS differences between LSTs ($M = 7.50$, SE ± 1.88) and HLTs ($M = 7.95$, SE ± 1.88). There was also no main effect of drug or significant drug × group interactions.

Analysis of CNRS scores showed a significant main effect of drug $F(1,18) = 14.78$, $p < .01$, with users reporting more symptoms with nicotine ($M = 1.90$, SE ± .19) compared to placebo ($M = 1.15$, SE ± .08). There was also a significant main effect of group, $F(1,18) = 6.44$, $p < .02$, with HLTs ($M = 1.80$, SE ± .15) reporting more nicotine-related symptoms than LSTs ($M = 1.25$, SE ± .15). Finally, follow-up of a significant drug × group interaction, $F(1,18) = 5.32$, $p < .03$, found that HLT users reported greater symptoms, $p < .000$, with nicotine ($M = 2.40$, SE ± .27) compared to placebo ($M = 1.20$, SE ± .12).

3.4. Vital signs

There was no significant effect of group, drug or drug × group interaction on SBP, DBP or HR. For DBP only, a planned comparison of drug × time revealed a significant difference, $p < .05$, between pre - and post-gum administration for nicotine only, indicating an increase in DBP ($MD = 4.77$ mm/mg Hg, SE ± 2.19) with nicotine.

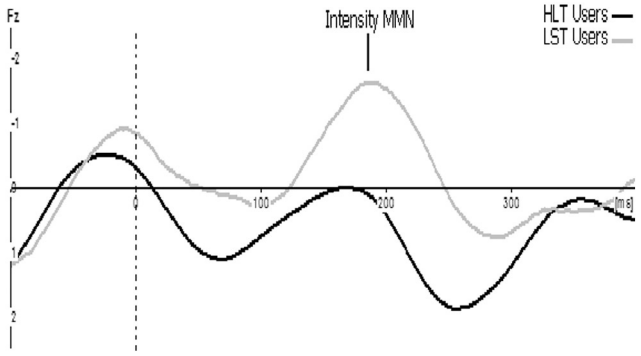

Fig. 6. Grand averaged frontal (Fz) MMN waveforms for HLT (black) and LST (gray) users elicited in response to intensity deviants, indicating a trend ($p = .06$) for reduced MMN amplitude in HLTs vs. LSTs.

4. Discussion

To the best of our knowledge, this is the first study to directly investigate the chronic effects of cannabis use on auditory processing independent of tobacco use. We compared auditory deviance detection, as indexed by the MMN ERP, in cannabis users with non-cannabis users, and in order to better examine the effect of chronicity of cannabis use, MMN was also examined in relation to amount/duration of cannabis use. Our hypothesis that cannabis users would exhibit diminished detection of acoustic deviants (reduced MMN amplitudes) compared to non-users was supported with duration deviants, and partially supported with gap and intensity deviants with trends towards attenuated MMNs in users at select sites. Moreover, our hypothesis that these auditory sensory deficits would be related to chronicity of cannabis use was supported with duration and gap deviants, and partially supported with intensity deviants with a trend towards attenuated MMN in relatively heavy, long-term (HLT) users compared to relatively light, short-term (LST) users. There were no differences between user groups or subgroups with frequency or location deviants. Acute nicotine was found to increase MMN amplitudes, compared to placebo, in response to location and frequency deviants, in the cannabis user individuals. Although these observations confirm that a cannabis use history significantly impairs early sensory processing independent of acute nicotine, effects in lighter users suggest that concurrent tobacco smoking in some cannabis users may mitigate sensory deficits.

Given that all participants reported cannabis use prior to 17 years of age, these results indicate that early and persistent cannabis smoking in an otherwise healthy, young adult population is associated with altered auditory sensory processing is a manner that may mimic impairment found in SZ patients. Our findings also demonstrate that duration and amount of use seems to modulate deviance detection, as HLT users were found to exhibit reduced MMNs compared to LST users. Both these effects were most robustly seen with duration deviants with some support with gap and intensity deviants. The different effects of cannabis on MMN types may be due to different generators, which may be more or less vulnerable to THC. Although Roser et al. (2010) and Rentzsch et al. (2011) also found support for impaired MMN generation in long term, heavy cannabis users, differences between their user and non-user groups could be attributed to differential nicotine use between groups and in the Roser study, controlling for nicotine use did indeed eliminate differences between groups. Both studies found no significant differences between user groups with respect to duration MMN but they did report reduced frequency MMN in cannabis users. Conversely, the current study did not find any between group differences with the frequency deviant and this may be due to study differences in frequency parameters. For our study, half the frequency deviants were a 10% increase and the other half were a 10% decrease of three sinusoidal partials of 500, 1000, and 1500 Hz, whereas the Roser study employed a single, but larger (20%) deviant increase from 1000 Hz (standard) to 1200 Hz (deviant), which would be slightly easier to detect within sensory memory and thus would generate a larger response. Conversely, our study used a very short (25 ms) duration deviant, which has a larger decrement from the standard (75 ms) compared to the Roser study ($\Delta = 40$ ms), which may help to explain differential findings. Finally, as 5 deviants were used, the ratio of standard/deviant probabilities are different than in the Roser study, which only used 2 deviants, and deviant probability is known to affect MMN generation (Fisher et al., 2011b).

In relation to the underlying neural mechanisms mediating cognitive impairment with cannabis use, it has been suggested that the MMN impairment in cannabis users might be related to cell toxicity (Roser et al., 2010), disruption in dopamine neurotransmission in cortical and subcortical regions involved in SZ (Kuepper et al., 2010) and/or by altering endogenous cannabinoid signaling. Generators of MMN originate from the auditory/temporal and frontal cortices, representing manifestation of pre-perceptual change detection and conscious

perception of stimulus change, respectively (Näätänen and Alho, 1995), and cannabis may affect either or both related processes. THC, the main psychoactive cannabinoid may play an important role in cognitive dysfunction through activation of presynaptic CB1 receptors in the hippocampus and the prefrontal cortex, areas which are known to be high in CB1 receptor density (Herkenham et al., 1990) and have important roles in cognitive function, specifically memory and executive function. Long-term cannabis users have been found to perform significantly worse than shorter term users and non-user controls on neuropsychological tests of memory and attention (Solowij et al., 2002). Long-term, heavy users may have considerably higher cannabinoid levels continuously present in the body which may continue to affect their cognitive performance even when they are not acutely intoxicated. In the current study, users were asked to abstain for at least 10 days before testing (average abstinence period was 14 days, verified by urine screening) to allow for the reduction of THC but not the complete elimination. Evidence for continuing performance impairments have been seen even after prolonged abstinence in chronic users (Solowij et al., 1995). These lasting cognitive impairments in sensory perception (Fisher et al., unpublished results), sensory memory (Rentzsch et al., 2011), attention (Roser et al., 2008a, 2008b) and behavioral performances measures (Solowij, 1998) suggests that THC is associated with deleterious long-term effects on the brain and behavior of cannabis users.

The sensory level impairments in auditory deviance detection in cannabis users found in this study are similar to the robust deficit found in SZ patients and in clinically unaffected family members of patients (Jessen et al. 2001; Michie et al., 2002). Of note, Rentzsch et al. (2011) recently found that cannabis user SZ patients did not differ from healthy control cannabis users, producing similar MMN deficits. Interestingly, in SZ, MMN amplitudes are consistently evident with duration deviants, more so than other types of deviants (Umbricht and Krljes, 2005), which is in line with our cannabis users findings. In patients, this is thought to be an impairment of auditory sensory memory and has been found to be related to the duration (Umbricht and Krljes, 2005) and the genetic aspect (Näätänen and Kähkönen, 2009) of the illness. Our findings add to the growing literature on ERP measures, including the P50, an index of sensory gating (Dissanayake et al., 2013) and the P300, an index of attention/novelty detection (Gallinat et al., 2012; Roser et al., 2008a, 2008b), as well as behavioral tasks of perception and attention (Solowij and Michie, 2007), which suggest that habitual cannabis use can negatively impact elementary sensory and early attentional processes, which are frequently impaired in SZ. Although cannabis use is neither a necessary nor sufficient cause of psychotic illness, our results also show some support for the "component cause" hypothesis, whereby heavy cannabis use in early adolescence is thought to induce SZ-like cognitive symptoms (Sewell et al., 2010). In this respect, it is important to note a recent breakthrough finding which showed that converters to SZ among at-risk individuals exhibited smaller duration MMNs than those in healthy controls (Sumiyoshi et al., 2013; Näätänen et al., 2015). However, we cannot establish a direct relationship between our MMN effects and SZ within the scope of this study and as development of SZ due to cannabis exposure seems to be specific to vulnerable populations (i.e., those with genetic predispositions; Arseneault et al., 2002), similar MMN studies need to be conducted in young adult cannabis users who are at risk for SZ.

It is important to note that cannabis users (and non-users) in the current study are mostly composed of undergraduate students and did not meet the criteria for cannabis abuse. This is in contrast to the Roser et al. (2010) study, which recruited cannabis abusers who met DSM-IV criteria and reported greater use and longer histories of use than the current study. The relatively small amounts used by our participants, which still produced significant deleterious effects, highlights the need to address the cognitive consequences of chronic marijuana smoking in youth. As cannabis users and non-users had similar education, age, gender and non-tobacco smoker status, these factors cannot account for the differences between groups. Also, measures of cannabis withdrawal did not differ between user subgroups, which suggests that the greater MMN impairment in HLTs cannot be attributed to increased withdrawal symptoms.

Our results partially confirmed our exploratory hypothesis that acute nicotine would enhance deviance detection in cannabis users, compared to placebo. Acute nicotine increased MMN amplitudes in cannabis users, who were found to have diminished MMNs compared to healthy controls. The positive effects of nicotine on MMN-indexed sensory discrimination demonstrate that alterations in cannabis users can be enhanced, or "normalized" by acute nicotine. This modulation was seen with frequency deviants and location deviants specifically, the former being limited to light short-term users and the latter being evident in all cannabis users. Although it is possible that the appearance of more nicotine adverse events in the heavy long-term users may have accounted for the absence of nicotine-enhanced frequency MMN in this group, both groups evidenced location MMN augmentation with nicotine. As MMNs elicited by different acoustic deviant features have different neural generators (Alho, 1995), it is possible that nAChR activity at these varying generators may be differentially impacted by length and degree of cannabis abuse and thus may exhibit varying sensitivity to acute nAChR agonist treatment.

The enhancement found with nicotine in the current study corresponds with previous work reporting enhanced MMNs to frequency deviants in cigarette smokers and non-smokers (Harkrider, and Hedrick, 2005) and elevated frequency MMN in non-smokers with a selective nicotinic acetylcholine receptor (nAChRs) agonist (Dunbar et al., 2007). Acute nicotine has also been found to increase MMN to interstimulus interval duration deviants in both smoking and non-smoking controls (Martin et al., 2009), visual MMN in non-smoking healthy controls (Fisher et al., 2010) and has also been found to "normalize" duration MMN in smoking SZ patients, which was diminished relative to controls (Dulude et al., 2010). Acute nicotine administration has also been reported to shorten intensity MMN latency in SZ, and MMN changes with nicotine were associated with changes with hallucination ratings (Fisher et al., 2012). Nicotine and α7 agonist treatment have also been found to increase MMN specifically in healthy volunteers with relatively reduced MMN amplitudes (Knott et al., 2014), which supports the current study findings. In patients, it is suggested that this effect may be mediated by activation of α7 nAChRs, the number and function of which is diminished in schizophrenia (Wallace and Porter, 2011). For cannabis users, it is suggested that nicotine-related improvements are also mediated by α7 nAChR activation, which has been associated with cognitive and behavioral improvements (Heishman et al., 1994). These previous findings and the current study support further research on nicotinic agonists as a possible treatment strategy for auditory processing impairments. Although this is the first study to assess the acute effects of nicotine on MMN in chronic cannabis users, the two previous studies which have assessed MMN in users have done so in long-term cigarette smokers (Roser et al., 2010; Rentzsch et al., 2011). As there is a vast amount of literature of the modulating effects of nicotine and cigarette smoking on cognitive function, especially in attentional and mnemonic domains (Rezvani and Levin, 2003; Newhouse et al., 2004; Jacobsen et al., 2007), and tobacco and cannabis are frequently used in combination, it is suggested that future studies assessing the cognitive effects of cannabis use do so independently of tobacco use.

Several limitations of this study have to be considered beyond the obvious weakness associated with the relatively small sample sizes used in this investigation. Information on duration, quantity and period of abstinence of cannabis use as well as on the use of other illegal drugs and nicotine in the past was obtained by verbal self-report. Although urine screens and CO tests were used as measures to help verify self-reports at the time of the study, future studies may want to measure over multiple time points prior to the study self-histories, discreet urine levels of THC and nicotine and their metabolites, and other drugs in the system, or consider analyzing the THC content of the cannabis that each participant consumes, as different strains of marijuana are

known to vary in their respective THC content (Burgdorf et al., 2011). Also, as there are no defined criteria for differentiating chronicity levels, our cannabis user group was split at the median on the composite score of quantity and duration of use, which, although pointing to a relationship between cannabis use chronicity and sensory memory impairment, resulted in subgroups with relatively high variability in cannabis use data. However, this approach is an established method for the determination of quantity and duration of cannabis use and is widely used in cannabis research (Roser et al., 2010; Solowij et al., 2002). Future studies may attempt a priori to recruit more homogenous light and heavy using groups with different selection criteria. Finally, nicotine effects were investigated only with a single dose and with oral nicotine, which is not absorbed as quickly as smoke-inhaled nicotine. Additional studies need to examine cigarette and cannabis smoking together in acute and chronic dosing designs.

5. Conclusion

In summary, the results of this study demonstrate that early and relatively light chronic cannabis users, with no history of tobacco use, evidence impairments of auditory deviance detection as measured by MMN. In addition, degree of cannabis use seems to be an important factor underlying MMN-indexed deviance detection impairment, as heavy long-term users had significantly smaller MMN than light short-term users. Although not supporting a direct causal influence, these chronicity-dependant MMN deficits are similar to those found in SZ patients, and they suggest that perturbations in early sensory processing with increasing cannabis use may be one cognitive pathway by which cannabis use increases risk for SZ in vulnerable youth, and they may be moderated by the central effects of nicotine.

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References

Alain, C., Bernstein, L.J., Cortese, F., Yu, H., Zipursky, R.B., 2002. Deficits in automatically detecting changes in conjunction of auditory features in patients with schizophrenia. Psychophysiology 39, 599–606.
Alho, K., 1995. Cerebral generators of mismatch negativity (MMN) and its magnetic counterpart (MMNm) elicited by sound changes. Ear Hear. 16 (1), 38–51.
Andreasson, S., Engstrom, A., Allebeck, P., Rydberg, U., 1987. Cannabis and schizophrenia: a longitudinal study of Swedish conscripts. Lancet 2 (8574), 1483–1486.
Arseneault, L., Cannon, M., Poulton, R., Murray, R., Caspi, A., Moffitt, T.E., 2002. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. Br. Med. J. 325, 1212–1213.
Bowers Jr., M.B., Mazure, C.M., Nelson, J.C., Jatlow, P.I., 1990. Psychotogenic drug use and neuroleptic response. Schizophr. Bull. 16, 81–85.
Braff, D.L., Light, G.A., 2004. Preattentional and attentional cognitive deficits as targets for treating schizophrenia. Psychopharmacology 174, 75–85.
Budney, A.J., Novy, P.L., Hughes, J.R., 1999. Marijuana withdrawal among adult seeking treatment for marijuana dependence. Addiction 94 (9), 1311–1322.
Burgdorf, J.R., Kilmer, B., Pacula, R.L., 2011. Heterogeneity in the composition of marijuana seized in California. Drug Alcohol Depend. 117, 59–61.
D'Souza, D.C., Abi-Saab, W.M., Madonick, S., Forselius-Bielen, K., Doersch, A., Braley, G., Gueorguieva, R., Cooper, T.B., Krystal, J.H., 2005. Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. Biol. Psychiatry 57, 594–608.
Dean, B., Sundram, S., Bradbury, R., Scarr, E., Copolov, D., 2001. Studies on [3H]CP-55940 binding in the human central nervous system: regional specific changes in density of cannabinoid-1 receptors associated with schizophrenia and cannabis use. Neurosci. 103, 9–15.
Dissanayake, D., Mason, R., Marsden, C., 2013. Sensory gating, cannabinoids and schizophrenia. Neuropharmacol. 67, 66–77.
Dulude, L., Labelle, A., Knott, V.J., 2010. Acute nicotine alteration of sensory memory impairment in smokers with schizophrenia. J. Clin. Psychopharmacol. 30 (5), 541–548.
Dunbar, G., Boeiginga, P., Demazieres, A., et al., 2007. Effects of TC-1734 (AZD3480), a selective neuronal nicotinic receptor agonist, on cognitive performance and the EEG of young healthy male volunteers. Psychopharmacology 191, 919–929.
Elvevag, B., Goldberg, T.E., 2000. Cognitive impairment in schizophrenia is the core of the disorder. Crit. Rev. Neurobiol. 14 (1), 1–21.
Family Interview for Genetic Studies, 1991. FIGS. Molecular Genetics Initiative: National Institute of Mental Health, Bethesda, MD.
Fernandez-Espejo, E., Viveros, M., Nunez, L., Ellenbroek, B.A., Rodriguez de Fonseca, F., 2009. Role of cannabis and endocannabinoids in the genesis of schizophrenia. Psychopharmacology 206, 531–549.
First, M., Spitzer, R., Gibbon, M., 1995. Structured Clinical Interview for DSM-IV: Patient and Non-Patient Version. Biometrics Research, New York State Psychiatric Institute, New York.
Fisher, D.J., Labelle, A., Knott, V.J., 2008. The right profile: mismatch negativity in schizophrenia with and without auditory hallucinations as measured by a multi-feature paradigm. Clin. Neurophysiol. 119, 909–921.
Fisher, D.J., Labelle, A., Knott, V.J., 2010. Auditory hallucinations and the P3a: attention switching to speech in schizophrenia. Biol. Psychol. 85, 417–423.
Fisher, D.J., Grant, B., Smith, D., Borracci, G., Labelle, A., Knott, V., 2011a. Effects of auditory hallucinations on the mismatch negativity, MMN in schizophrenia as measured by a modified 'optimal' multi-feature paradigm. Int. J. Psychophysiol. 79 (2), 311–315.
Fisher, D.J., Grant, B., Smith, D.M., Knott, V.J., 2011b. Effects of deviant probability on the 'optimal' multi-feature mismatch negativity (MMN) paradigm. Int. J. Psychophysiol. 79, 311–315.
Fisher, D., Grant, B., Smith, D., Borracci, G., Labelle, A., Knott, V., 2012. Nicotine and the hallucinating brain: effects on mismatch negativity (MMN) in schizophrenia. Psychiatry Res. 196, 181–187.
Fletcher, P.C., Honey, G.D., 2006. Schizophrenia, ketamine and cannabis: evidence of overlapping memory deficits. Trends Cogn. Sci. 10 (4), 167–174.
Freedman, R., Adams, C.E., Leonard, S., 2000. The α7-nicotinic acetylcholine receptor and the pathology of hippocampal interneurons in schizophrenia. J. Chem. Neuroanat. 20 (3), 299–306.
Gallinat, J., Rentzsch, J., Roser, P., 2012. Neurophysiological effects of cannabinoids: implications for psychosis research. Curr. Pharm. Des. 18, 4938–4949.
Gaoni, Y., Mechoulam, R., 1964. Isolation, structure and partial synthesis of an active constituent of hashish. J. Am. Chem. Soc. 86, 1646–1647.
Green, M.F., 1996. What are the functional consequences of neurocognitive deficits in schizophrenia? Am. J. Psychiatry 153, 321–330.
Green, M.F., Kern, R.S., Braff, D.L., Mintz, J., 2000. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff". Schizophr. Bull. 26 (1), 119–136.
Hall, W., Degenhardt, L., 2000. Cannabis use and psychosis: a review of clinical and epidemiological evidence. Aust. N. Z. J. Psychiatry 34, 26–34.
Harkrider, A., Hedrick, M., 2005. Acute effect of nicotine on auditory gating in smokers and non-smokers. Hear. Res. 202, 114–128.
Heishman, S., Taylor, R., Henningfield, J., 1994. Nicotine and smoking: a review of effects on human performance. Exp. Clin. Psychopharmacol. 2, 1–51.
Henquet, C., Murray, R., Linszen, D., van Os, J., 2005. The environment and schizophrenia: the role of cannabis use. Schizophr. Bull. 31 (3), 608–612.
Herkenham, M., Lynn, A.B., Little, M.D., Johnson, M.R., Melvin, L.S., de Costa, B.R., Rice, K.C., 1990. Cannabinoid receptor localization in brain. Proc. Natl. Acad. Sci. U. S. A. 87, 1932–1936.
Hirayasu, Y., Potts, G.F., O'Donnell, B.F., Kwon, J.S., Arakaki, H., Akdaq, S.J., et al., 1998. Auditory mismatch negativity in schizophrenia: topographic evaluation with a high-density recording montage. Am. J. Psychiatr. 155, 1281–1283.
Hukkanen, J., Jacob, P., Benowitz, N.L., 2005. Metabolism and disposition kinetics of nicotine. Pharmacological reviews 57, 79–115.
Inami, R., Kirino, E., Inoue, R., Arai, H., 2005. Transdermal nicotine administration enhances automatic auditory processing reflected by mismatch negativity. Pharmacol. Biochem. Behav. 80, 453–461.
Inami, R., Kirino, E., Inove, R., et al., 2007. Nicotine effects on mismatch negativity in schizophrenia patients. Neuropsychobiol. 56, 64–72.
Jacobsen, L.K., Pugh, K.R., Constable, R.T., Westerveld, M., Mencl, W.E., 2007. Functional correlates of verbal memory deficits emerging during nicotine withdrawal in abstinent adolescent cannabis users. Biol. Psychiatry 61, 31–40.
Javitt, D.C., 2000. Intracortical mechanisms of mismatch negativity dysfunction in schizophrenia. Audiol. Neuroontol. 5, 207–215.
Javitt, D.C., Shelley, A.M., Ritter, W., 2000. Associated deficits in mismatch negativity generation and tone matching in schizophrenia. Clinical Neurophysiology 111 (10), 1733–1737.
Javitt, D.C., Doneshka, P., Zylberman, L., Ritter, W., Vaughan Jr., H.G., 1993. Impairment of early cortical processing in schizophrenia: an event-related potential confirmation study. Biol. Psychiatry 33, 513–519.
Jessen, F., Fries, T., Kucharski, C., Nishimura, T., Hoenig, K., Maier, W., Heun, R., 2001. Amplitude reduction of the mismatch negativity in first-degree relatives of patients with schizophrenia. Neuroscience letters 309 (3), 185–188.
Johansson, E., Halldin, M.M., 1989. Urinary excretion half-life of delta 1-tetrahydrocannabinol-7-oic acid in heavy marijuana users after smoking. J. Anal. Toxicol. 13, 218–223.
Kasai, K., Nakagome, N., Itoh, K., Koshida, I., Hata, A., Iwanami, A., Fukuda, M., Kato, N., 2002. Impaired cortical network for preattentive detection of change in speech sounds in schizophrenia: a high resolution event-related potential study. Am. J. Psychiatry 159, 546–553.
Kawakubo, Y., Kamio, S., Nose, T., Iwanami, A., Nakagome, K., Fukuda, M., Kato, N., Rogers, M.A., Kasai, K., 2007. Phonetic mismatch negativity predicts social skills acquisition in schizophrenia. Psychiatry Res. 152, 261–265.
Knott, V., Impey, D., Choueiry, J., Smith, D., de la Salle, S., Saghir, S., …, Labelle, A., 2015. An acute dose, randomized trial of the effects of CDP-Choline on Mismatch Negativity (MMN) in healthy volunteers stratified by deviance detection level. Neuropsychiatr. Electrophysiol. 1 (1), 1–23.
Knott, V., Impey, D., Philippe, T., Smith, D., Choueiry, J., Salle, S., Dort, H., 2014. Modulation of auditory deviance detection by acute nicotine is baseline and deviant dependent in

healthy nonsmokers: a mismatch negativity study. Human Psychopharmacology: Clinical and Experimental 29 (5), 446–458.
Kuepper, R., Morrison, P.D., van Os, J., Murray, R.M., Kenis, G., Henquet, C., 2010. Does dopamine mediate the psychosis-inducing effects of cannabis? A review and integration of findings across disciplines. Schizophr. Res. 121 (1–3), 107–117.
LeVeke, F.M., Koethe, D., 2008. Cannabis and psychiatric disorders: it is not only addiction. Addict. Biol. 13, 264–275.
Leweke, F.M., Schneider, U., Thies, M., Munte, T.F., Emrich, H.M., 1999. Effects of synthetic delta9-tetrahydrocannabinol on binocular depth inversion of natural and artificial objects in man. Psychopharmacology 142 (3), 230–235.
Leweke, F.M., Gerth, C.W., Klosterkötter, J., 2004. Cannabis associated psychosis: current status of research. C.N.S. Drugs 18, 895–910.
Light, G.A., Braff, D.L., 2005. Mismatch negativity deficits are associated with poor functioning in schizophrenia patients. Arch. Gen. Psychiatry 62, 127–136.
Light, G.A., Williams, L.E., Minow, F., Sprock, J., Rissling, A., Sharp, R., Swerdlow, N.R., Braff, D.L., 2010. Electroencephalography (EEG) and event-related potentials (ERP) with human participants. Curr. Protoc. Neurosci. 1–22.
Linszen, D., van Amelsvoort, T., 2007. Cannabis and psychosis: an update on course and biological plausible mechanisms. Curr. Opin. Psychiatry 20 (2), 116–120.
Mahgoub, M., Keun-Hang, S., Sydorenko, V., Ashoor, A., Kabbani, N., Kury, L., Sadek, B., Howarth, C., Isaev, D., Galaduri, S., Oz, M., 2013. Effects of cannabidol on the function of α7-nicotinic acetylcholine receptors. Eur. J. Pharmacol. 720, 310–319.
Margolese, H.C., Malchu, L., Negrete, J.C., Tempier, R., Gill, K., 2004. Drug and alcohol use among patients with schizophrenia and related psychoses: levels and consequences. Schizophr. Res. 67 (2–3), 157–166.
Martin, L.F., Davalos, D.B., Kisley, M.A., 2009. Nicotine enhances automatic temporal processing as measured by the mismatch negativity waveform. Nicotine Tob. Res. 11 (6), 698–706.
Martinez-Arevalo, M.J., Calcedo-Ordonez, A., Varo-Prieto, J.R., 1994. Cannabis consumption as a prognostic factor in schizophrenia. Br. J. Psychiatry 164, 679–681.
Matsuda, L.A., Lolait, S.J., Brownstein, M.J., Young, A.C., Bonner, T.I., 1990. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature 346, 561–564.
Michie, P.T., 2001. What has MMN revealed about the auditory system in schizophrenia? Int. J. Psychophysiol. 42, 177–194.
Michie, P.T., Innes-Brown, H., Todd, J., Jablensky, A.V., 2002. Duration mismatch negativity in biological relatives of patients with schizophrenia spectrum disorders. Biol. Psychiatry 52, 749–758.
Näätänen, R., 1995. The mismatch negativity: a powerful tool for cognitive neuroscience. Ear Hear. 16, 6–18.
Näätänen, R., Ahlo, K., 1997. Mismatch negativity—the measure for central sound representation accuracy. Audiol. Neurootol. 2, 341–353.
Näätänen, R., Alho, K., 1995. Generators of electrical and magnetic mismatch responses in humans. Brain Topogr. 7, 315–320.
Näätänen, R., Kähkönen, S., 2009. Central auditory dysfunction in schizophrenia as revealed by the mismatch negativity (MMN) and its magnetic equivalent MMNm: a review. Int. J. Neuropsychopharmacol. 12, 125–135.
Näätänen, R., Pakarinen, S., Rinne, T., Takegata, R., 2004. The mismatch negativity (MMN): towards the optimal paradigm. Clin. Neurophysiol. 115 (1), 140–144.
Näätänen, R., Shiga, T., Asano, S., Yabe, H., 2015. Mismatch negativity (MMN) deficiency: a break-through biomarker in predicting psychosis onset. Int. J. Psychophysiol. 95, 338–344.
Newhouse, P., Potter, A., Singh, A., 2004. Effects of nicotinic stimulation on cognitive performance. Curr. Opin. Psychopharmacol. 4, 36–46.
Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh Inventory. Neuropsychologia 9 (1), 97–113.
Radhakrishnan, R., Wilkinson, S., D'Souza, D., 2014. Gone to pot — a review of the association between cannabis and psychosis. Front. Psychiatry 5, 1–24.
Rentzsch, J., Buntebar, E., Stadelmeier, A., Gallinat, J., Jockers-Scherubl, M.C., 2011. Differential effects of chronic cannabis use on preattentional cognitive functioning in abstinent schizophrenic patients and healthy subjects. Schizophr. Res. 130 (1), 222–227.
Rezvani, A.H., Levin, E.D., 2003. Nicotine interactions with the NMDA glutaminergic antagonist dizocilpine and attentional function. Eur. J. Pharmacol. 465, 83–90.
Roser, P., Juckel, G., Rentzsch, J., Nadulski, T., Gallinat, J., Stadelmann, A., 2008a. Effects of acute oral Δ^9-tetrahydrocannabinal event-related potential in healthy volunteers. Eur. Neuropsychopharm. 18, 569–577.
Roser, P., Stadelmann, A.M., Arning, L., Gallinat, J., Epplen, J.T., Juckel, G., 2008b. Acute effects of D9-tetrahydrocannabinol on the auditory event-related mismatch negativity depending on genetic variations in the dysbindin, neuregulin and G72 gene. Int. J. Neuropsychopharmacol. 11 (1), 256.
Roser, P., Della, B., Norra, C., Uhl, I., Brune, M., Juckel, G., 2010. Auditory mismatch negativity deficits in long-term heavy cannabis users. Eur. Arch. Psychiatry Clin. Neurosci. 260, 491–498.
Schwartz, R.H., Gruenewald, P.J., Khtxner, M., Fedio, P., 1989. Short-term memory impairment in cannabis-dependent adolescents. Am. J. Dis. Child. 143, 1214–1219.
Sewell, R.A., Skosnik, P.D., Garcia-Sosa, I., Ranganathan, M., D'Souza, D.C., 2010. Behavioral, cognitive and psychophysiological effects of cannabinoids: relevance to psychosis and schizophrenia. Rev. Bras. Psiquiatr. 32 (1), 15–30.
Shelley, A.M., Ward, P.B., Catts, S.V., Michie, P.T., Andrews, S., McConaghy, N., 1991. Mismatch negativity: an index of a preattentive processing deficit in schizophrenia. Biol. Psychiatry 30, 1059–1062.
Skosnik, P.D., Spatz-Glenn, L., Park, S., 2001. Cannabis use is associated with schizotypy and attentional disinhibition. Schizophr. Res. 48 (1), 83–92.
Solowij, N., 1998. Cannabis and Cognitive Functioning. Cambridge University Press, Cambridge.
Solowij, N., Michie, P.T., 2007. Cannabis and cognitive dysfunction: parallels with endophenotypes of schizophrenia? J. Psychiatry Neurosci. 32 (1), 30–52.
Solowij, N., Michie, P.T., Fox, A.M., 1995. Differential impairment of selective attention due to frequency and duration of cannabis use. Biol. Psychiatry 37, 731–739.
Solowij, N., Stephens, R.S., Roffman, R.A., Babor, T., Kadden, R., Miller, M., Christiansen, K., McRee, B., Vendetti, J., 2002. Cognitive functioning of long-term heavy cannabis users seeking treatment. JAMA 287, 1123–1131.
Sumiyoshi, T., Miyanishi, T., Seo, T., Higuchi, Y., 2013. Electrophysiological and neuropsychological predictors of conversion to schizophrenia in at-risk subjects. Front. Behav. Neurosci. 7, 148.
Sundram, S., 2006. Cannabis and neurodevelopment: implications for psychiatric disorders. Hum. Psychopharmacol. Clin. Exp. 21, 245–254.
Todd, J., Michie, P.T., Schall, U., Karayanidis, F., Yabe, H., Näätänen, R., 2008. Deviant matters: duration, frequency, and intensity deviants reveal different patterns of mismatch negativity reduction in early and late schizophrenia. Biol. Psychiatry 63, 58–64.
Turner, W.M., Tsuang, M.T., 1990. Impact of substance abuse on the course and outcome of schizophrenia. Schizophr. Bull. 16, 87–95.
Umbricht, D., Krljes, S., 2005. Mismatch negativity in schizophrenia: a metaanalysis. Schizophr. Res. 76, 1–23.
van Os, J., Bak, M., Bijl, R.V., et al., 2002. Cannabis use and psychosis: a longitudinal population-based study. Am. J. Epidemiol. 156, 319–327.
Viveros, M.P., Marco, E.M., File, S.E., 2006. Nicotine and cannabinoids: parallels, contrasts and interactions. Neurosci. Biobehav. Rev. 30, 1161–1181.
Wallace, T., Porter, R., 2011. Targeting the nicotinic alpha7 acetylcholine receptor to enhance cognition in disease. Biochem Pharmacology 32, 891–903.
Weil, A.T., 1970. Adverse reactions to marihuana. Classification and suggested treatment. N. Engl. J. Med. 282, 997–1000.
Youn, T., Park, H.-J., Kim, J.-J., Kim, M.S., Kwon, J.S., 2003. Altered hemispheric asymmetry and positive symptoms in schizophrenia: equivalent current dipole of auditory mismatch negativity. Schizophr. Res. 59, 253–260.
Zavitsanou, K., Garrick, T., Huang, X.F., 2004. Selective antagonist [3H] SR 141716A binding to cannabinoid CB1 receptors is increased in the anterior cingulate cortex in schizophrenia. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 28, 355–360.