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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