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# Cannabis abuse is associated with better emotional memory in schizophrenia: A functional magnetic resonance imaging study

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ABSTRACT

In schizophrenia cannabis abuse/dependence is associated with poor compliance and psychotic relapse. Despite this, the reasons for cannabis abuse remain elusive, but emotions may play a critical role in this comorbidity. Accordingly, we performed a functional magnetic resonance imaging study of emotional memory in schizophrenia patients with cannabis abuse (dual-diagnosis, DD). Participants comprised 14 DD patients, 14 non-abusing schizophrenia patients (SCZ), and 21 healthy controls (HC) who had to recognize positive and negative pictures while being scanned. Recognition of positive and negative emotions was prominently impaired in SCZ patients, relative to HC, while differences between DD and HC were smaller. For positive and negative stimuli, we observed significant activations in frontal, limbic, temporal and occipital regions in HC; in frontal, limbic and temporal regions in DD; and in temporal, parietal, limbic and occipital regions in the SCZ group. Our results suggest that emotional memory and prefrontal lobe functioning are preserved in DD relative to SCZ patients. These results are consistent with previous findings showing that cannabis abuse is associated with fewer negative symptoms and better cognitive functioning in schizophrenia. Longitudinal studies will need to determine whether the relative preservation of emotional memory is primary or secondary to cannabis abuse in schizophrenia.
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## 1. Introduction

In schizophrenia, the lifetime prevalence of substance use disorders (SUD) approaches 50%; this estimate represents a three- to five-fold increased risk relative to the general population (Regier et al., 1990; Cantor-Graae et al., 2001). In decreasing order, schizophrenia patients abuse alcohol, cannabis, and stimulants, if we exclude tobacco (Regier et al., 1990). Drug preferences are influenced by sample age. Indeed, a recent meta-analysis by Koskinen et al. (2010) reported that alcohol use disorder was more common in older schizophrenia populations, while younger patients (< 30 years) more frequently suffered from cannabis use disorder (lifetime risk up to 45%).

As other psychoactive substance, cannabis negatively interferes with the course and treatment of schizophrenia. Cannabis abuse/dependence is indeed associated with higher psychotic relapses and hospitalization rates, more severe positive symptoms, non-adherence to antipsychotic therapy, an earlier age of schizophrenia onset, as well as more suicide attempts (Cantor-Graae et al., 2001; Dervaux et al., 2003; Zammit et al., 2008; Foti et al., 2010).

Despite these debilitating consequences, the reasons motivating cannabis smoking in schizophrenia remain elusive. Preliminary evidence suggests that emotions may play a role in this comorbidity. For instance, a study by Kirkpatrick et al. (1996) showed that the deficit syndrome of schizophrenia (presence of primary, prominent and enduring negative symptoms) is associated with lower rates of lifetime SUD. Moreover, two recent meta-analyses by our group underlined that relative to non-addicted schizophrenia patients, those dependent on cannabis express fewer negative symptoms, including anhedonia and blunting of affect (Potvin et al., 2006), and that they experience more severe depressive symptoms (Potvin et al., 2007a). Consistently, the most frequently reported reasons for substance use in schizophrenia are to experience a high and to cope with stress, anxiety and dysphoria (Green et al., 2004; Dekker et al., 2009). In a complementary fashion, other investigations have shown that cannabis abuse/dependence is associated with better pre-morbid

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adjustment levels and better social skills in schizophrenia (Arndt et al., 1992; Salyers and Mueser, 2001; Yucel et al., 2012). Whether these differences are the cause or the consequence of substance abuse in schizophrenia remains a matter of debate. One way or another, mounting evidence suggests that there are significant emotional differences between schizophrenia patients with and without cannabis smoking, and that these emotional differences contribute to their use of cannabis. Altogether, these observations have led Blanchard et al. (1999, 2000) to hypothesize that schizophrenia patients use psychoactive substances (including cannabis) in order to regulate their emotions.

To our knowledge, no study has examined the neural correlates of emotional experience in schizophrenia patients with substance abuse, apart from two previous studies by our group. This is of major concern given that approximately half of schizophrenia patients struggle with lifetime SUD, particularly cannabis use disorders, for which the median lifetime rate was 27.1% in the meta-analysis of Koskinen et al. (2010). Our preliminary studies addressed this question by investigating negative emotion processing between schizophrenia patients with and without SUD (Mancini-Marie et al., 2006; Potvin et al., 2007a). The results of both studies suggest a preserved functioning of the medial prefrontal cortex in dual-diagnosis patients compared to non-addicted schizophrenia patients. Nevertheless, these studies presented certain limitations that we aimed to address in the current study: (1) the inclusion of dual-diagnosis patients abusing mixed substances (cannabis and/or alcohol), (2) the lack of a control group of healthy subjects, (3) the restricted use of negatively charged stimuli, and finally (4) the specific investigation of emotion experience.

Reliable evidence suggests that there are significant deficits in facial affect *identification* in schizophrenia, and that emotional *expression* is flattened in these patients (Tremeau, 2006; Kohler et al., 2010). By contrast, numerous experimental studies have examined emotional *experience* in schizophreni through the use of images and videos, and a recent synthesis of this literature has revealed subtle, if any, differences in the reported *experience* of emotion in schizophrenia patients compared to controls (Kring and Caponigro, 2010). This pattern of findings is inconsistent with the flattening of affect and anhedonia observed by raters during psychiatric interviews (Kring and Caponigro, 2010). As a means of explaining this discrepancy between laboratory and clinical settings, some authors relied on the vast literature documenting significant explicit memory impairments in schizophrenia (Leavitt and Goldberg, 2009) to propose that this disorder may be associated with impairments in recalling (not experiencing) emotional events, and to propose that this may explain why patients seem emotionally indifferent in clinical settings (Kring and Moran, 2008). Therefore, our group decided to specifically examine the memory of emotional stimuli in schizophrenia, and its neural correlates. Behaviorally, most studies that have looked at emotional memory tasks have reported poorer performances of schizophrenia patients relative to controls (Sergerie et al., 2010; Becerril and Barch, 2011; Lakis et al., 2011). As for neuroimaging findings, the limited literature in schizophrenia displayed reduced brain activations in dorsolateral prefrontal cortex, hippocampus and amygdala during the recall of emotional stimuli (Whalley et al., 2009; Sergerie et al., 2010; Becerril and Barch, 2011; Lakis et al., 2011; Wolf et al., 2011).

Thus, the aim of the present study was to investigate the neural correlates of emotional memory in schizophrenia patients with and without cannabis use disorder, relative to healthy participants. We opted to investigate the memory of negative (sad, fearful, disgusting) and positive (agreeable, happy) stimuli, which are both part of our everyday experiences. We expected to observe an increased emotional experience and better recognition accuracy of both negative and positive material in dual-diagnosis patients compared to non-abusing schizophrenia patients. Generally, in terms of cerebral functions, we envisaged that dual-diagnosis patients would present a more typical pattern of brain activations for both conditions relative to non-abusing schizophrenia patients; that is, greater activations of the limbic system and prefrontal cortex.

## 2. Methods

### 2.1. Participants

Twenty-eight outpatients who met DSM-IV criteria for schizophrenia (American Psychiatric Association, 1994) and who were in a stable phase of illness (no hospitalization within the last 2 months and no change in antipsychotic medication within the last month) were divided into two groups: 14 patients diagnosed with cannabis use disorder (last 6 months) (dual-diagnosis–DD) and 14 patients without SUD (SCZ). We also added 21 healthy controls (HC). Participants were men; aged between 18 and 55 years; with no concomitant neurological, axis I or axis II disorders, including schizophreniform or schizo-affective disorders; and no contra-indications for functional magnetic resonance imaging (fMRI). Importantly, DD patients did not abuse any other psychoactive substance.

Patients were evaluated by experienced psychiatrists using DSM-IV criteria (American Psychiatric Association, 1994). Controls were screened with the non-patient edition of the *Structured Clinical Interview for DSM-IV* (Spitzer et al., 1992). Symptoms severity was rated with the *Positive and Negative Syndrome Scale* (PANSS) (Kay et al., 1987). Participants were required to abstain from smoking cannabis during the day of their scheduled appointment. Prior to being scanned, patients were carefully screened for signs of cannabis intoxication (e.g. impaired motor coordination, conjunctival dilatation, euphoria) or withdrawal (e.g. nervousness, mood swings, headaches, appetite or sleep disturbances) by a psychiatrist (MD) experienced in drug addiction diagnoses. Participants were also required to complete a self-report questionnaire assessing the frequency of their cannabis consumption.

In agreement with the *Declaration of Helsinki*, written informed consent was obtained from each participant. The study was approved by the ethics committees of the *Fernand-Seguin Research Center* and the *Réseau de Neuroimagerie du Québec*.

### 2.2. Experimental procedure

First, participants passively viewed positive, negative, and neutral pictures taken from the International Affective Picture System (IAPS) while in the scanner (Lang et al., 1988). Although participants were aware that a memory task would follow, they were not explicitly told to remember the images. After a 15-min delay, participants were administered the memory task, which consisted of viewing blocks of positive, negative, and neutral pictures similarly to the incidental encoding task. Half of the stimuli in each block originated from the incidental encoding task while the other half were never seen before. During this memory task, participants were asked to determine, by pressing the correct button, which of the stimuli were previously seen. To assess the participants' subjective emotional responses, immediately at the end of the fMRI session, participants were again-presented with the image blocks and were asked to rate them as a whole on a scale ranging from 0 (absence of any emotional reaction) to 8 (strongest emotion ever felt in one's lifetime) the intensity of experienced emotion (please refer to Fig. 1).

### 2.3. fMRI data acquisition

We recorded blood oxygenation level dependent (BOLD) signals using a single-shot, gradient-recalled echo-planar imaging sequence (repetition time (TR)= 3000 ms, echo time (TE)=30 ms, flip angle=90°, matrix size=64 × 64 voxels, voxel size=3.5 × 3.5 × 3.5 $mm^3$) on a Siemens TRIO MRI system at 3.0 T at the *Functional Neuroimaging Unit at the University of Montreal Geriatric Institute*. We then registered the functional volumes to individual high-resolution co-planar anatomical images taken during the same scanning session session (see Lakis et al., 2011).

### 2.4. fMRI data analysis

We analyzed fMRI data using statistical parametric mapping software (SPM5: Wellcome Department of Cognitive Neurology, London, UK) according to the methods outlined by Friston (1995). The functional images were realigned to the mean volume of the run to correct for artifacts due to minor head movements, high-pass filtered, spatially normalized into the standardized brain template, and spatially smoothed with a three-dimensional isotropic Gaussian kernel (8 mm full width half-maximum) to improve signal-to-noise ratio.

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